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From Pandemic to Persistence: Obesity, Immunity, and Next-Gen COVID-19 Vaccines

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Abstract: The COVID-19 pandemic, though no longer classified as a global emergency, persists as a major public health challenge in 2025 due to the continued emergence of SARS-CoV-2 variants with enhanced transmissibility and immune evasion. This paper reviews the evolving epidemiology of COVID-19, the critical interplay between obesity and disease severity, and advances in precision vaccination and therapeutics. Epidemiological and meta-analytic evidence highlights obesity as a significant independent risk factor for infection, hospitalization, ICU admission, mechanical ventilation, and mortality, underpinned by mechanisms such as immune dysfunction, chronic low-grade inflammation, and obesity-related comorbidities. Moreover, obesity is shown to impair vaccine-induced immune responses, complicating long-term protection. In parallel, updated mRNA and protein-subunit vaccines, alongside emerging monoclonal antibody and antiviral strategies, reflect the shift toward precision medicine tailored to vulnerable populations, particularly the immunocompromised. While monoclonal antibody efficacy has been undermined by viral evolution, novel agents such as pemivibart and vilobelimab demonstrate promise in targeted settings. Collectively, the findings underscore the importance of sustained surveillance, equitable vaccine distribution, integrated obesity prevention, and personalized medical interventions. As SARS-CoV-2 continues to adapt, long-term mitigation will require scientific innovation, public health vigilance, and commitment to global health equity.

Keywords: *COVID-19, SARS-CoV-2 Variants, Obesity and COVID-19, Precision Vaccination, Immune Dysfunction, Chronic Inflammation, Personalized Medicine, Public Health Surveillance.*

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I. INTRODUCTION

Since its emergence in late 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has profoundly reshaped global health, economies, and societies. While initial responses were dominated by urgent containment strategies, rapid vaccine development, and therapeutic innovation, the subsequent years have revealed the virus's remarkable capacity for persistence through continual genetic evolution. In February 2025, more than 777 million confirmed cases and over 7 million deaths have been recorded globally, underscoring COVID-19's sustained impact despite declining surveillance and public attention [1]. The circulation of novel variants such as XEC, JN.1, and KP.2 has further complicated mitigation efforts by enhancing transmissibility and facilitating immune evasion, thereby necessitating ongoing adaptation of vaccination and treatment strategies.

Parallel to viral evolution, host-related factors have played a critical role in shaping disease severity. Obesity, in particular, has emerged as one of the most significant risk factors for adverse outcomes in COVID-19. Epidemiological evidence consistently demonstrates a dose-response relationship between elevated body mass index (BMI) and the risks of hospitalization, intensive care admission, mechanical ventilation, and mortality. Mechanistic studies reveal that obesity contributes to impaired immune responses, chronic systemic inflammation, and a heightened prevalence of comorbidities, all of which synergistically worsen disease progression. Importantly, obesity has also been shown to compromise vaccine-induced immunity, raising concerns about long-term protection in this population.

In response to these dual challenges of viral evolution and host vulnerability, public health strategies have increasingly shifted toward precision approaches. Updated mRNA and protein-subunit vaccines, tailored to circulating variants, alongside emerging therapeutics such as pemivibart and vilobelimab, reflect the move toward personalized prevention and treatment. At the same time, the integration of COVID-19 monitoring into existing respiratory surveillance systems highlights the need for sustained vigilance.

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This paper examines the persistence of COVID-19 in 2025 through the lens of evolving viral variants, obesity-related pathogenesis, and the rise of precision vaccination and therapeutics. By synthesizing epidemiological, biological, and clinical evidence, it underscores the necessity of sustained innovation, equitable vaccine access, and obesity-targeted interventions to mitigate the long-term consequences of the pandemic.

II. THE EPIDEMIOLOGY OF SARS-COV-2 INFECTION IN 2025

The SARS-CoV-2 test positivity rate, measured through both sentinel and systematic virological surveillance, is a reliable indicator of how wide the virus is circulating in communities. Importantly, this metric is not influenced by broader reductions in overall disease monitoring activities. Since SARS-CoV-2 tracking has been integrated into existing respiratory disease surveillance systems, more countries are now reporting cases to the Global Influenza Surveillance and Response System (GISRS). Detailed global and national data on SARS-CoV-2 PCR percent positivity can be accessed through the World Health Organization's (WHO) integrated influenza and respiratory virus surveillance dashboard.

Globally, during the first four weeks of 2025 (January), SARS-CoV-2 positivity rates in samples collected through systematic surveillance stayed stable, averaging around 6–7% [2]. These figures are based on a weekly average of 69,932 processed specimens, with data submitted by 103 countries that reported at least once during this period [3]. In the same timeframe, over 147,000 new cases and more than 4,500 deaths were recorded. Cumulatively, as of 2 February 2025, there have been more than 777.4 million confirmed cases and over 7 million deaths worldwide [4].

Wastewater surveillance suggests that true infection levels may be 2 to 19 times higher than reported case numbers, highlighting the underestimation caused by reduced testing and reporting [5]. Despite these declines, COVID-19 continues to pose a major public health risk. The WHO urges member states not to scale back existing COVID-19 response systems but instead to preserve critical measures such as early warning and surveillance systems, timely reporting, variant monitoring, rapid clinical interventions, vaccination of high-risk groups, improved ventilation, and consistent public communication (https://data.who.int/dashboards/covid19/cases?n=o, https://data.who.int/dashboards/covid19/deaths?n=o).

- *Respiratory Impairment*

Obesity exerts profound effects on pulmonary mechanics, mainly through excess fat deposition around the thoracic cavity and abdomen. This additional load reduces lung compliance, impedes diaphragmatic movement, and lowers functional residual capacity [7]. Such alterations compromise ventilation and gas exchange, increasing the likelihood of hypoventilation and hypoxemia during acute respiratory illness.

Clinical investigations support these observations. Peters et al. demonstrated that individuals with higher BMI exhibit significant declines in expiratory reserve volume and lung compliance, factors that predispose them to respiratory distress [8]. Similarly, Salome et al. reported increased airway resistance and ventilation–perfusion mismatch in obese patients, further elevating the work of breathing [9].

Another factor is the higher prevalence of obstructive sleep apnea (OSA) in individuals with obesity. OSA is characterized by intermittent hypoxia and impaired ventilatory control, both of which are independent risk factors for worse COVID-19 outcomes [10]. When combined with reduced pulmonary reserve, these mechanical and physiological limitations create a vulnerable respiratory profile, explaining why obese individuals are more likely to develop severe hypoxemia and acute respiratory failure when infected with SARS-CoV-2.

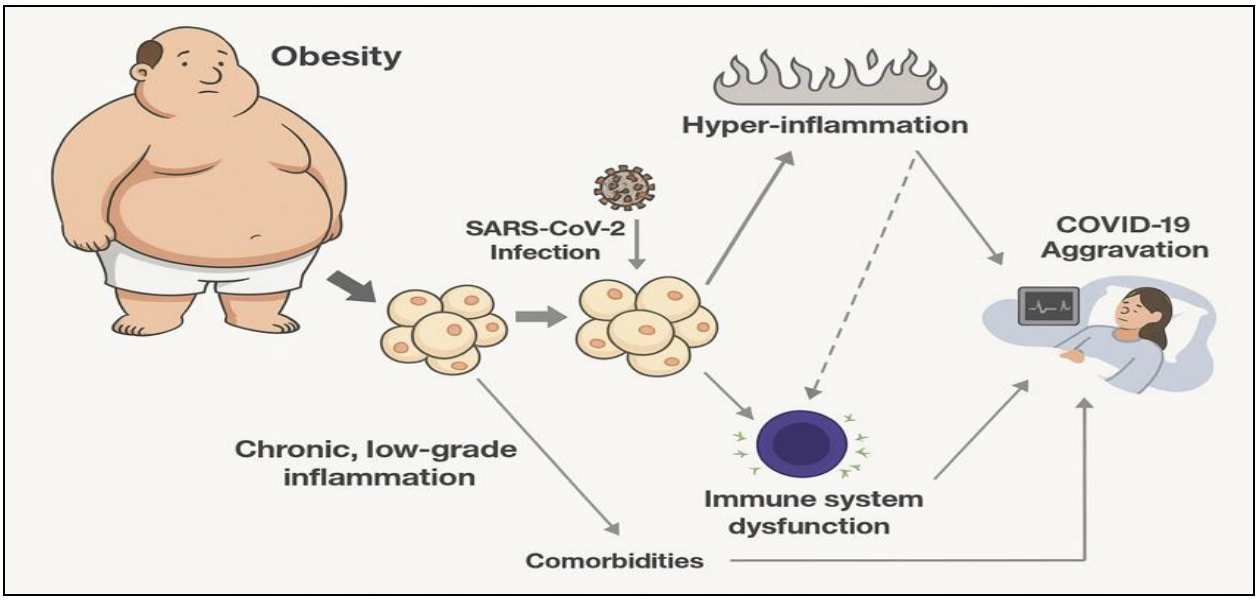

Fig 1 The Complex Relationship Between Obesity and COVID-19 Highlights Significant Implications for Health Outcomes. COVID-19 Stands for Coronavirus Disease 2019.

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III. UNRAVELING THE BIOLOGICAL LINK BETWEEN COVID-19 AND OBESITY

The increased risk of severe COVID-19 among individuals with obesity can be attributed to several biological mechanisms. These include impaired immune defenses, persistent low-grade inflammation, and the frequent coexistence of chronic health conditions (Figure 1).

➢ *Immune Dysfunction*

The innate immune system, a crucial first-line defense against pathogens, is often compromised in people with overweight or obesity. This reduced capacity weakens the body's ability to counter viral infections. Tong et al. examined 82 recovered COVID-19 patients, including 45 with BMI ≥25 kg/m², and found that those with higher BMI had significantly weaker antibody responses—lower antibody levels at 3 months, reduced avidity, and fewer spike-positive B cells at 13 months [15]. In a separate study, Madruga et al. analyzed 50 hospitalized patients requiring low-flow oxygen therapy and noted that overweight and obese individuals had markedly fewer mature natural killer (NK) cells compared to those of normal weight [16].

Vaccine studies support this pattern. Van der Klaauw et al. conducted a prospective longitudinal study involving 28 individuals with severe obesity (BMI >40 kg/m²) and 41 with normal BMI (18.5–24.9 kg/m²). Six months after vaccination, 55% of the severely obese group had undetectable neutralizing antibodies, compared with only 12% of the normal-weight group ($P<0.001$). The neutralizing ability was also considerably lower in those with severe obesity [17].

Jang et al. further demonstrated that SARS-CoV-2 receptors are highly expressed in adipose tissue, facilitating viral entry and replication while promoting inflammatory mediator release [18]. This process disrupts both humoral and cellular immune responses, resulting in abnormal lymphocyte differentiation and premature immune cell exhaustion. Collectively, rapid antibody decline, NK cell impairment, and lymphocyte dysfunction compromise viral clearance and increase the risk of severe outcomes.

A player in this response is the NLRP3 inflammasome, a regulator of innate immunity. Studies show that NLRP3 activation is heightened in patients with severe COVID-19, leading to excessive IL-1β release and fueling cytokine storms [19]. Targeting this pathway with inhibitors such as colchicine has shown therapeutic promise, particularly for overweight and obese patients [20–22].

➢ *Chronic, Low-Grade Inflammation*

Persistent low-grade inflammation is a hallmark of obesity [23]. Because COVID-19 progression is strongly tied to inflammatory cascades—including cytokine storm [24]—this chronic inflammatory state may worsen the acute immune response triggered by SARS-CoV-2. Consequently, individuals with obesity face elevated risks of cytokine release syndrome, acute respiratory distress syndrome (ARDS), and multi-organ failure.

Supporting evidence comes from Saccon et al., who conducted postmortem analyses of 47 adipose tissue samples from individuals who died of COVID-19. They observed sustained expression of pro-inflammatory genes such as IFNA, IL-6, and CCL2 [25]. Similarly, Fessler et al. found a significant correlation between higher BMI and elevated levels of IL-6, TNF-α, CRP, ferritin, IL-12, and IL-13 in 60 COVID-19 patients [26].

Reiterer et al. provided further insights in a large study of 3,854 hospitalized patients, demonstrating that SARS-CoV-2 infects adipose tissue and triggers systemic inflammation, insulin resistance, and hyperglycemia—all of which predispose patients to ARDS and higher mortality [27]. Elevated leptin, common in obesity, may also amplify inflammatory responses after infection [28].

➢ *Obesity, Comorbidities, and COVID-19*

Comorbid conditions substantially increase the risk of severe COVID-19 outcomes. Patients with multiple comorbidities experience higher mortality rates than those with other major illnesses, including cancer and cardiovascular disease (CVD) [29]. Obesity, in particular, predisposes individuals to a range of chronic conditions. Visceral adiposity contributes to insulin resistance, chronic inflammation, and metabolic dysfunction, which drive the development or worsening of CVD, type 2 diabetes, and several cancers (notably breast, colon, endometrial, liver, and kidney). Obesity is also linked to endocrine disorders such as polycystic ovary syndrome and thyroid disease, as well as mental health problems like depression and anxiety. Other complications include sleep apnea, liver dysfunction, and kidney impairment [30].

The clustering of these comorbidities in obese patients creates a highly vulnerable profile, significantly increasing the probability of severe complications and mortality when infected with SARS-CoV-2.

➢ *COVID-19 Prevention in 2025*

Although global concern has diminished, COVID-19 continues to spread and cause substantial morbidity and mortality (https://data.who.int/dashboards/covid19/deaths?n=o). Mass vaccination campaigns remain the cornerstone of prevention. Since 2021, more than 13 billion vaccine doses have been administered worldwide. Safety monitoring conducted by the WHO and other regulatory bodies has consistently confirmed that adverse reactions are rare. COVID-19 vaccines remain safe and effective across populations, continuing to serve as the most reliable strategy for limiting disease burden.

IV. COVID-19 VACCINES

➢ *COVID-19 Vaccination Strategies*

Since their introduction in late 2020, COVID-19 vaccines have been the foundation of the global response to the pandemic. They have dramatically lowered the risk of infection, hospitalization, and death. By early 2025, more

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than 13 billion vaccine doses had been given worldwide, covering populations in over 180 countries [31]. This makes the COVID-19 vaccination campaign one of the largest public health undertakings in history.

Health agencies such as the World Health Organization (WHO) and national regulatory authorities continue to closely monitor vaccine safety. Results consistently show that serious side effects are extremely rare, while the protection vaccines offer is significant [32]. This has strengthened public health messages that the benefits of vaccination far outweigh the risks.

As the virus has changed, vaccines have also been updated. New "variant-adapted" boosters have been designed to provide stronger protection against the most concerning variants. Studies show that these boosters restore immunity, which naturally declines over time, and they greatly improve the body's ability to fight off severe illness [33].

Importantly, vaccine recommendations have been updated to reflect the evolving science. In August 2024, the U.S. Food and Drug Administration (FDA) approved updated 2024–2025 COVID-19 vaccines, with specific guidance on who should receive them [CDC, 2025; WHO, 2025]:

- Children aged 6 months to 4 years: require multiple doses, including at least one dose of the updated 2024–2025 vaccine.
- Children aged 5 to 11 years: may receive one dose of the updated vaccine.
- People aged 12 years and older: may receive one dose of the updated vaccine.
- Adults aged 65 years and older, as well as those who are moderately or severely immunocompromised, may receive a second dose six months after their first. Immunocompromised individuals may also receive additional doses following consultation with their healthcare provider.

Despite this clear guidance, not all regions have had equal access to vaccines. Many low- and middle-income countries face shortages due to cost, distribution issues, or supply chain barriers [34]. This global inequality leaves millions of people vulnerable. To minimize the impact, public health strategies increasingly prioritize high-risk groups—including people with obesity, diabetes, and heart disease—since these groups face the greatest danger from severe COVID-19 [35].

➢ *Therapeutic Approaches*

While vaccines are the best defense against infection, treatments are vital for those who still become sick. Over the past four years, doctors have developed a wide range of therapeutic approaches to reduce the severity of COVID-19 and improve survival [42, 43].

Antiviral drugs are among the most important. Medicines such as remdesivir, molnupiravir, and the oral combination therapy nirmatrelvir/ritonavir (Paxlovid) directly interfere with the virus's ability to replicate inside the body [36]. When given early—usually within the first few days of infection—these antivirals can shorten illness, reduce viral load, and significantly lower the risk of hospitalization.

Monoclonal antibodies were another breakthrough early in the pandemic. These laboratory-made antibodies helped neutralize the virus and provided rapid protection to high-risk patients. However, as the virus evolved, many new variants became resistant to these therapies, reducing their usefulness [37].

For patients with severe or critical illness, especially those needing oxygen or ventilation, immunomodulatory drugs are essential. These treatments do not target the virus itself but rather the body's excessive immune reaction. Corticosteroids, particularly dexamethasone, remain the standard of care because they reduce inflammation and improve survival in patients with advanced disease [38]. In addition, drugs that block interleukin-6 (IL-6), such as tocilizumab, have been shown to help by calming the dangerous "cytokine storm" that can damage organs [39].

Scientists are also exploring new therapies that specifically target inflammatory pathways. One promising direction involves blocking the NLRP3 inflammasome, a protein complex that drives uncontrolled inflammation. This pathway is often overactive in people with obesity, making them more prone to severe illness. Early research suggests that NLRP3 inhibitors—such as colchicine—may reduce life-threatening inflammation, though these treatments are still largely experimental [40].

➢ *Preventive and Supportive Measures*

Even with vaccines and treatments, non-medical strategies remain important. Preventive measures such as wearing high-quality masks in crowded settings, maintaining physical distancing during outbreaks, and ensuring good ventilation indoors can significantly reduce transmission [41]. Improving air quality through filtration and airflow systems is especially important in schools, offices, and healthcare facilities.

Surveillance and monitoring are also key pillars of pandemic control. PCR testing, case reporting, and wastewater analysis allow health authorities to track how the virus is spreading, detect early outbreaks, and identify new variants [42, 43]. These systems act as "early warning signals," helping governments prepare responses and guide vaccine updates. Public communication and education remain critical. Clear and transparent messaging builds trust, combats misinformation, and encourages people to follow prevention guidelines. Combining vaccines, treatments, preventive measures, and surveillance creates a layered defense strategy, ensuring that COVID-19 is managed as an ongoing public health challenge rather than an uncontrolled global crisis.

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V. CONCLUSION

The COVID-19 pandemic has transitioned from a global emergency into a persistent and evolving public health challenge. Driven by continual viral mutation and the emergence of new variants such as XEC, JN.1, and KP.2, SARS-CoV-2 has maintained its foothold despite decreased public awareness and testing. These newer variants, characterized by enhanced transmissibility and immune evasion, have prompted a shift in public health strategies—moving toward precision vaccination and targeted therapeutic approaches, such as pemivibart for immunocompromised populations. Meanwhile, the intersection of obesity and COVID-19 continues to be a critical area of concern, with robust evidence demonstrating that obesity significantly increases susceptibility to severe disease, weakens immune response, and complicates vaccine efficacy. Addressing this dual burden through integrated surveillance, equitable vaccine distribution, personalized medical interventions, and public health policies focused on obesity prevention will be key to mitigating long-term consequences. As the virus adapts, so must we—with sustained vigilance, scientific innovation, and a commitment to global health equity.

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