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Letter to the Editor

Psychological and Behavioral Determinants of Vaccine Efficacy: Insights from SARS-CoV-2 and Implications for Future Pandemics

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Dear Editor,

Despite widespread vaccination, SARS-CoV-2 continues to circulate in waves, highlighting the need to better understand the multifactorial determinants of vaccine efficacy. Beyond its immediate health impact, the pandemic has intensified skepticism toward vaccines – a phenomenon with historical precedent dating back to Edward Jenner (1). Current hesitancy often arises from adverse effects, the accelerated pace of vaccine development, competition among pharmaceutical companies, and the proliferation of misinformation. While some concerns are evidence-based, many reflect perceived opacity from developers and political influence, as well as rumors.

We hypothesize that negative attitudes toward vaccination may directly compromise immune responses. Psychological stress, anxiety, and depression can alter the neuroimmune axis, reducing both cellular and humoral immunity. This may partly explain suboptimal vaccine responses during COVID-19 and could influence outcomes in future pandemics.

Vaccine efficacy is influenced by genetics, pre-existing conditions, and sex (2, 3). Emerging evidence suggests that mental state and attitude are equally important. Neuroendocrine immunology and psychoimmunology studies show that chronic stress impairs T-cell function and antibody production, while acute stress may transiently enhance immune activity (Figure 1) (4-11). Research consistently demonstrates that psychological states such as stress, anxiety, depression, and even transient mood can significantly impact immune components by modulating neuroendocrine pathways (5, 6). Stress hormones and catecholamines can disrupt dendritic cell activity and T-cell activation, while chronic low-grade inflammation further compromises vaccine-induced immunity (11-17). While acute stress can temporarily boost some immune functions, like the movement of immune cells, chronic stress consistently leads to widespread immunosuppression (9). Long-term stress is linked to a reduction in natural killer (NK) cells and lymphocytes, both of which are critical for the body's defense (10, 11). mRNA vaccines such as Pfizer-BioNTech and Moderna elicit robust immune responses, but optimal protection depends on psychological and physiological conditions (12-15). Distrust or negative perceptions may reduce antibody titers and weaken cellular immunity over time.

The intricate interplay between psychological stressors and the immune system involves multiple pathways. For instance, stress hormones like cortisol can inhibit the production and function of cytokines such as interleukin-2 (IL-2), crucial for T-cell proliferation (16). Similarly,

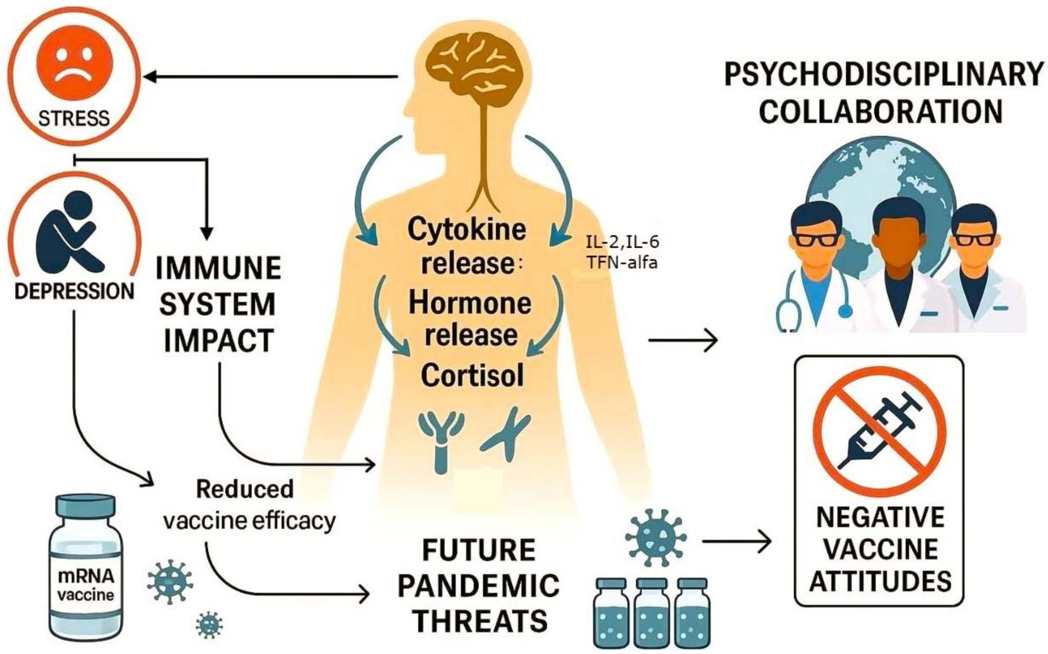

Figure 1. Conceptual Framework for the Impact of Psychological States on Vaccine Efficacy

catecholamines released during stress can modulate the activity of dendritic cells, impairing their ability to present antigens effectively, thus weakening the activation of T-cells and subsequent adaptive immune responses (17). Chronic stress can also induce the release of pro-inflammatory cytokines like IL-6 and TNF-α, which, in a persistent state, can lead to a state of chronic low-grade inflammation, thereby impairing the body's ability to mount an effective immune response to vaccines (18). Negative public attitudes, combined with viral evolution, may undermine efforts to control potential pandemics caused by viruses such as SARS-CoV-2, influenza A, Lassa fever, Ebola, Marburg, Monkeypox, and dengue (19-21). These pathogens pose a risk of increased lethality or long-term health sequelae. COVID-19 has illustrated how multiple factors can converge to create a perfect storm: economic disruption, reduced research capacity, vaccine hesitancy, and stress-related immune suppression collectively heighten vulnerability to emerging pathogens. The combination of public mistrust weakened immune defenses, and potentially more virulent viruses could lead to pandemics that are both more severe and longer lasting.

Isolating the effect of attitudes on immunity is challenging due to confounders such as socioeconomic status, healthcare access, and cultural factors. Prospective cohort studies are needed to establish causal links between psychological state, immune function, and infection outcomes. Interdisciplinary collaboration across immunology, psychology, neurology, microbiology, and virology is essential. Culturally sensitive interventions targeting mental health and public trust could enhance vaccine efficacy and strengthen global pandemic preparedness.

Authors' Contribution

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Competing Interests

The authors declare that they have no conflict of interests.

Ethical Approval

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