Identification of Vulnerable Populations for Novel Coronavirus Infection and Prospects for Prevention and Treatment Postprint

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Abstract

The COVID-19 pandemic has inflicted severe damage on human health and the global economy. Health-related vulnerable populations exhibit compromised immune function, resulting in insufficient vaccine protective efficacy and higher risks of severe disease and death following SARS-CoV-2 infection. Currently, there remains a lack of sufficiently targeted preventive and therapeutic drugs for SARS-CoV-2 infection. In the context of China's Class B infectious disease management policy, vulnerable populations have become the key focus of epidemic prevention and control efforts. Therefore, individual immunity and prevention strategies for vulnerable populations should be further optimized, requiring additional preventive measures beyond vaccines, such as long-acting neutralizing antibodies. Based on this, this article will review the identification of vulnerable populations, characteristics of immune function, and prevention methods, to provide a reference for prevention and treatment strategies for health-related vulnerable populations in China, with the hope that more suitable preventive drugs for vulnerable populations can be developed in the future to reduce the risk of SARS-CoV-2 infection in these groups.

Full Text

Preamble

Identification of COVID-19 Infection in Vulnerable Populations and Its Prevention and Treatment Perspectives

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Abstract The COVID-19 pandemic has devastated human health and the global economy. Health-related vulnerable populations exhibit diminished immune function, leading to insufficient vaccine protection and higher risks of severe illness and death following SARS-CoV-2 infection. Currently, there remains a lack of adequately targeted drugs for COVID-19 prevention and treatment. Under China's "Category B disease management" policy, vulnerable populations have become the priority focus for epidemic prevention and control. Therefore, individualized immunization and prevention strategies for these populations require further optimization. Beyond vaccination, additional preventive measures such as long-acting neutralizing antibodies are needed. This review summarizes the identification, immune function characteristics, and prevention strategies for vulnerable populations, providing references for prevention and control strategies for health-related vulnerable populations in China. We anticipate the future development of more suitable preventive drugs to reduce COVID-19 risk among vulnerable groups.

[**Key words**] COVID-19; Vulnerable populations; Long-acting neutralizing antibody; Prevention; Review

Introduction

On December 26, 2022, China's National Health Commission announced the reclassification of COVID-19 from "novel coronavirus pneumonia" to "novel coronavirus infection." The Joint Prevention and Control Mechanism subsequently issued the "Overall Plan for Implementing Category B Management for COVID-19," which took effect on January 8, 2023. Under this new framework, China's prevention and control objectives focus on "protecting health and preventing severe disease," with particular emphasis on vulnerable populations including the elderly, children, pregnant women, and patients with underlying medical conditions. The Joint Prevention and Control Mechanism also issued the "Health

Service Plan for Key COVID-19 Populations," highlighting the critical importance of managing vulnerable groups.

Vulnerability factors encompass both socioeconomic and health-related dimensions. Vulnerable populations exhibit compromised immune function and reduced vaccine response rates, resulting in inadequate vaccine protection and necessitating supplementary preventive measures such as long-acting neutralizing antibodies. This review aims to summarize clinical evidence on health-related vulnerable populations during the COVID-19 pandemic to inform prevention and treatment strategies in China.

1 Identification of Vulnerable Populations

Vulnerable populations are generally defined as those at higher risk in health risk assessments. Due to variations in disease burden, age structure, and healthcare systems, the composition of vulnerable populations differs across countries and regions. Based on existing clinical evidence and domestic and international COVID-19 guidelines, China has established a simplified and practical assessment system that categorizes infection risk into three levels based on age, underlying disease status, and vaccination history: high-risk (score 4-6), medium-risk (score 2-3), and low-risk (score 0-1), marked with red, yellow, and green respectively .

The high-risk group represents the primary focus during the COVID-19 pandemic. However, clinicians should understand that this scoring tool was designed for grassroots implementation and recognize the complexity of patient populations. For patients with underlying diseases, both unstable and severe but stable conditions carry elevated risks. Additionally, individuals who completed full vaccination more than six months ago face gradually increasing susceptibility over time, with higher overall risk compared to those within six months of vaccination. These considerations require further refinement based on clinical practice and recent evidence.

2.1 Impaired Immune Function in Vulnerable Populations

SARS-CoV-2 is an enveloped positive-sense RNA virus whose spike (S) protein is critical for viral entry. Current vaccines primarily target the receptor-binding domain of the S protein. However, vaccine protection depends on active immune responses that activate innate and adaptive immunity to generate sufficient neutralizing antibodies, memory B cells, and memory T cells.

The immune system undergoes "inflammaging" with age, characterized by elevated baseline levels of pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) in older adults. Concurrently, "immunosenescence" leads to blunted immune responses to pathogenic threats. Both innate and adaptive immune functions decline with age, including reduced pathogen recognition, chemotaxis, and phagocytosis by macrophages, NK cells, and neutrophils; decreased T cell receptor

diversity; thymic replacement by adipose tissue after age 60, reducing naïve T cell reserves; and diminished B cell antibody secretion. These changes increase susceptibility to SARS-CoV-2.

China's immunocompromised population is growing and represents a major vulnerable group, including allogeneic hematopoietic stem cell transplant recipients, solid organ transplant recipients, cancer patients undergoing chemotherapy, and patients with rheumatic diseases requiring long-term immunosuppression. These individuals develop iatrogenic cellular and humoral immune deficiency from chronic immunosuppressive therapy. For example, China performs over 20,000 organ transplants annually, and recipients often have severe underlying conditions pre-transplant. Chronic diseases such as hypertension, diabetes, and obesity also impair immune function through inflammatory damage and immune imbalance, increasing COVID-19 risk. Hemodialysis patients exhibit persistent immune inflammation due to uremic toxins and complement activation, which increase TLR2/TLR4 expression and pro-inflammatory cytokines while impairing phagocytosis, antigen presentation, and T cell activation, ultimately reducing adaptive immune responses.

Studies show that tumor patients susceptible to SARS-CoV-2 exhibit specific defects in immune cell responses to the S1-RBD domain, with only a small fraction mounting effective immune responses. Similarly, only a minority of immunocompromised patients develop antibodies after vaccination. Disease-related (autoimmune diseases, hematologic malignancies) or treatment-related (anti-tumor drugs, immunosuppressants) immunosuppression increases SARS-CoV-2 susceptibility.

Pregnancy represents a unique immune state where the maternal immune system must maintain tolerance to the allogeneic fetus while preserving antimicrobial defenses. Hormonal changes during pregnancy reduce dendritic cells, monocytes, and activation of macrophages, T lymphocytes, and B lymphocytes, potentially increasing viral infection risk.

In summary, impaired immune function in vulnerable populations prevents adequate active immune responses, increasing susceptibility to SARS-CoV-2 and reducing vaccine efficacy compared to the general population. These populations also face higher risks of hospitalization, severe disease, and death.

2.2 Hospitalization, Severe Disease, and Mortality Risk in Vulnerable Populations

COVID-19 exhibits significant heterogeneity, ranging from mild to critical illness. Evidence consistently shows that older adults face higher risks of severe disease and mortality. During the Omicron wave in South Africa, individuals over 60 had significantly higher severe disease risk than those aged 19-24 [OR=11.5, 95%CI (2.8, 47.0)]. CDC data as of January 11, 2023, showed that adults over 65 accounted for 75.5% of COVID-19 deaths. According to China's National Health Commission, between December 8, 2022, and January 12, 2023,

hospitals reported 59,938 COVID-related deaths, with 90.1% aged 65 and older (average age 80.3 years) and 56.5% aged 80 and older. Over 90% of decedents had underlying conditions, primarily cardiovascular disease, advanced cancer, cerebrovascular disease, respiratory disease, metabolic disease, and renal insufficiency. Multiple studies confirm that more comorbidities correlate with higher severe disease risk.

Immunocompromised individuals have suppressed humoral and/or cellular immunity due to health status or immunosuppressive medications, increasing severe COVID-19 risk. Studies show that even when vaccinated, hematologic malignancy patients have increased risks of COVID-related hospitalization [RR=3.13, 95%CI (1.68, 7.08)] and severe disease [RR=2.27, 95%CI (1.18, 5.19)], while solid organ transplant recipients have significantly increased ICU admission and mortality rates.

Growing evidence confirms that pregnant women face substantially increased severe COVID-19 risk. CDC data show that among women aged 15-44, after adjusting for age, race, and comorbidities, pregnant women had increased risks of ICU admission [aRR=3.0, 95%CI (2.6, 3.4)], invasive ventilation [aRR=2.9, 95%CI (2.2, 3.8)], ECMO [aRR=2.4, 95%CI (1.5, 4.0)], and death [aRR=1.7, 95%CI (1.2, 2.4)] compared to non-pregnant women.

Overall, vulnerable populations face significantly higher risks of critical illness and mortality from COVID-19.

2.3 Symptoms and Quality of Life in Vulnerable Populations

Impaired immune function prevents rapid viral clearance, with SARS-CoV-2 persisting for weeks to months in vulnerable individuals. This prolonged viral carriage delays treatment of underlying conditions. Infection-related isolation and antiviral medications also interfere with scheduled treatments (radiation, chemotherapy) and surgeries, affecting quality of life and survival. Additionally, post-COVID-19 “long COVID” syndrome significantly impacts quality of life, with meta-analyses identifying anxiety/depression and pain/discomfort as the most common long-term problems.

2.4 Public Health Impact of COVID-19 in Vulnerable Populations

Vulnerable populations not only have higher infection risk but also contribute disproportionately to healthcare burden. A case study reported a woman with chronic lymphocytic leukemia and hypogammaglobulinemia who shed infectious virus for 105 days, with slow clearance during treatment, posing transmission risks. Research indicates that persistent infection in immunosuppressed individuals may facilitate evolution of more transmissible or pathogenic variants, further straining healthcare systems.

3 Pharmacological Prevention for COVID-19 in Vulnerable Populations

China has a large population of vulnerable individuals, including substantial numbers of elderly and patients with chronic diseases. Mathematical modeling shows that increasing vaccination rates among those over 60, widespread use of antiviral drugs, and strict non-pharmacological interventions (NPIs) such as hand hygiene, masking, and social distancing could significantly reduce hospitalizations, ICU admissions, and deaths, easing healthcare burden. Researchers recommend comprehensive strategies combining vaccination, antiviral drugs, and NPIs, with urgent efforts to increase vaccination rates among those aged 60 and above.

Since their development, SARS-CoV-2 vaccines have played a crucial role in preventing infection, severe disease, hospitalization, and death. Shanghai data show that among symptomatic patients over 60, two to three doses of inactivated vaccine provided 90.15% protection against severe disease. However, vaccine hesitancy due to safety concerns remains high in vulnerable populations, and immunocompromised individuals often have inadequate immune responses and insufficient antibody production even after vaccination. A meta-analysis of 42 studies found seroconversion rates after two vaccine doses were 99% [95%CI (98%, 100%)] in immunocompetent individuals, 92% [95%CI (88%, 94%)] in solid tumor patients, 78% [95%CI (69%, 95%)] in immune-mediated inflammatory disease patients, 64% [95%CI (50%, 76%)] in hematologic malignancy patients, and only 27% [95%CI (16%, 42%)] in transplant recipients. This inadequate antibody production reduces vaccine effectiveness in vulnerable populations, necessitating additional preventive strategies beyond vaccination.

3.1 Pre-Exposure Prophylaxis

Monoclonal antibodies (mAbs) have proven effective for preventing infectious diseases. Current COVID-19 treatment guidelines recognize specific monoclonal neutralizing antibodies as preventive and therapeutic agents that block viral entry into host cells. Antibody half-life (t1/2) critically affects efficacy, with longer-acting antibodies being more suitable for pre-exposure prophylaxis. Clinically available neutralizing antibodies ranked by t1/2 from shortest to longest are: bebtelovimab (11.5 days), bamlanivimab (20.9 days), etesevimab (32.6 days), casirivimab (31.8 days), imdevimab (26.9 days), sotrovimab (49 days), tixagevimab (87.9 days), and cilgavimab (82.9 days). The tixagevimab/cilgavimab combination has the longest t1/2, and the PROVENT study demonstrated its ability to reduce symptomatic COVID-19 risk in immunocompromised individuals with good safety profiles. Its protective effects have been confirmed in hematologic malignancy patients, organ transplant recipients, and other immunocompromised individuals. The combination is approved for pre-exposure prophylaxis in specific populations in the United States, European Union, Japan, and other countries.

3.2 Post-Exposure Prophylaxis

Vaccinated individuals with exposure to SARS-CoV-2 remain at risk for breakthrough infection. Monoclonal antibodies can be used for both pre- and post-exposure prophylaxis. Several neutralizing antibody combinations have been evaluated for post-exposure prophylaxis, including bamlanivimab/etesevimab, casirivimab/imdevimab, and tixagevimab/cilgavimab. However, the first two are ineffective against Omicron variants and have been restricted by the FDA.

Multiple antiviral drugs are used for COVID-19 treatment, including molnupiravir, remdesivir, favipiravir, tenofovir, nirmatrelvir/ritonavir, and azvudine. Drawing from HIV prevention strategies, these agents could be considered for post-exposure prophylaxis in immunocompromised individuals, though clear evidence of benefit is lacking.

Additionally, over 85% of COVID-19 patients in China receive traditional Chinese medicine. Agents such as glycyrrhiza, pelargonium, and forsythia have demonstrated in vitro anti-coronavirus activity and could be considered for prophylaxis.

4 Summary and Outlook

As a narrative review, this article's literature search strategy was based on relevant references encountered during the authors' work rather than following strict systematic review and meta-analysis requirements. While this limitation will be addressed in future research, the clinical evidence and recommendations provided remain valuable for COVID-19 prevention and control in high-risk populations.

Following the implementation of Category B management, vulnerable populations face significant challenges in COVID-19 prevention and control, warranting close clinical attention. Current research lacks sufficient evidence regarding vaccine efficacy and safety in vulnerable populations, and clinical benefit data for post-exposure prophylaxis drugs remain inadequate. Future clinical research should conduct more in-depth and refined studies on COVID-19 vaccines and therapeutic agents to develop more suitable prevention and treatment protocols that can effectively mobilize active immune responses and reduce infection and severe disease risks in vulnerable populations.

From a management perspective, high-risk individuals require clear documentation of their underlying conditions and health status to ensure personal protection measures. Efforts should promote comprehensive vaccination, particularly when underlying diseases are stable, to achieve full coverage among vulnerable populations. For those unable to receive or requiring delayed vaccination, long-acting neutralizing antibodies should be considered as supplementary prevention. Additionally, ensuring timely treatment after infection is essential to achieve the "protect health, prevent severe disease" objective and ultimately overcome the pandemic.

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