Incidence, Risk Factors, and Outcomes of Severe Breakthrough COVID-19 Infections among Hospitalized Patients in Africa

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ABSTRACT

Background: The emergence of breakthrough COVID-19 infections among fully vaccinated individuals has raised concerns regarding vaccine efficacy and the impact of emerging variants. This systematic review aims to investigate the incidence, risk factors, and outcomes of severe breakthrough infections among hospitalized patients in Africa.

Materials and Methods: A comprehensive literature search was conducted from 2021 to 12 April 2024 across major academic databases, including PubMed, Google Scholar, and Scopus, to identify outcome studies on severe breakthrough COVID-19 infections among hospitalized patients in Africa. Data extraction and synthesis were performed to analyze the incidence, risk factors, and outcomes of severe breakthrough COVID-19 infections.

Results: Findings revealed a concerning incidence of breakthrough infections, particularly notable during the Omicron variant period, emphasizing ongoing transmission risks within vaccinated populations. Risk factors such as younger age (16-35) years, and incomplete vaccination schemas were consistently associated with severe breakthrough infections, guiding risk stratification and targeted interventions. Clinical characteristics highlighted a notable proportion of severe cases, underscoring the importance of continued vigilance and preventive measures.

Conclusion: Breakthrough COVID-19 infections in Africa, particularly in countries like Egypt and South Africa reveal varying incidence rates, risk factors, and outcomes. These studies underscore the importance of understanding the dynamics of breakthrough infections and their implications for public health interventions. While studies in Egypt, and South Africa provide valuable insights into the factors contributing to breakthrough infections and their outcomes, there is a notable gap in research in other African countries. Conducting similar studies in other African countries is crucial to tailor vaccination strategies and public health interventions to the local context. By understanding the incidence, risk factors, and outcomes of breakthrough infections, policymakers and healthcare practitioners can better allocate resources, implement targeted interventions, and mitigate the impact of COVID-19 on the population. Additionally, research in other African countries can contribute to global knowledge on breakthrough infections, particularly in understudied regions, and inform broader strategies for controlling the spread of COVID-19 worldwide. Therefore, conducting a study on breakthrough infections in other African countries is essential to fill this gap in knowledge and enhance the effectiveness of COVID-19 response efforts in a country and beyond.

Keywords: Incidence; Risk factors; Outcomes; Severe COVID-19, Infections, Hospitalized, Patients in Africa.

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Introduction

Mechanism of COVID-19 breakthrough infections

The coronavirus disease (COVID-19), stemming from the novel coronavirus SARS-CoV-2 and initially identified by Chinese authorities in late 2019, swiftly burgeoned into a global health crisis, rapidly traversing borders and continents. What commenced as a localized outbreak in Wuhan,

China, soon burgeoned into a worldwide pandemic, affecting countries across Asia and beyond.

On January 30, 2020, the World Health Organization (WHO) declared the COVID-19 outbreak a Public Health Emergency of International Concern (PHEIC), signifying the urgent need for global attention and cooperation to address the escalating crisis. Within a matter of weeks, the virus's relentless spread prompted the WHO to elevate its classification, declaring COVID-19 a pandemic on March 11, 2020. This designation underscored the severity and widespread impact of the disease, highlighting the imperative for coordinated international efforts to mitigate its effects and contain transmission.

The declaration of a pandemic underscored the gravity of the situation, triggering unprecedented public health responses worldwide. Governments implemented a spectrum of measures ranging from lockdowns and travel restrictions to widespread testing and vaccination campaigns in a bid to curb transmission and safeguard public health.1

Epidemiology of COVID-19 breakthrough infections

The emergence of SARS-CoV-2 and its subsequent evolution into various variants has been a significant factor in the trajectory of the COVID-19 pandemic, leading to millions of deaths worldwide. These variants often exhibit distinct characteristics such as enhanced transmission or immune escape, impacting the effectiveness of public health measures and vaccination efforts. While several variants of concern have been identified, including some originating from the African continent like Beta, Eta, and Omicron, many African countries have been underrepresented in global genomic surveillance efforts.[20]

The COVID-19 situation in Africa presents a puzzle, with lower reported cases and mortality rates compared to other continents than expected18 despite being the second most populous continent. Africa, with an estimated 17.2% of the world's population, accounts for only 5% of total cases and 3% of mortality as of August 01, 2020. South Africa and Egypt lead in reported cases. Importantly, these countries are among those conducting the highest number of tests, crucial in confirming cases. However, testing rates remain lower than global counterparts, with South Africa leading in Africa with 2.9 million tests, followed by Morocco (1.2 million), Ethiopia (422,000), and Ghana (391,000). Limited access to testing resources, including reagents and personnel, hampers efforts. Ghana's innovative approach of pooling samples has increased efficiency, yet challenges persist due to high test costs and resource availability. Antibody testing suggests a significant portion of the population may have been infected, potentially 10%-20%, with studies revealing 40% seroprevalence in certain populations. Misattributed deaths may further mask the true impact of COVID-19. Despite lower reported cases, challenges in testing accessibility and accurate data collection underscore the need for continued vigilance and improved testing infrastructure to effectively manage the pandemic in Africa.[17]

A recent meta-analysis addressing a significant gap in our comprehension of COVID-19's effects on the African continent has unveiled crucial insights. Compiled from seven separate studies and encompassing data from 4,499 patients, the study sheds light on the clinical characteristics and outcomes of COVID-19 patients in Africa. Key findings from the analysis include firstly, the predominance of male patients among those infected with COVID-19 in Africa is notable, with 68.8% of cases occurring in males. This gender disparity aligns with trends observed in other regions and underscores the need for further research into potential biological and sociodemographic factors contributing to this phenomenon. Secondly, the study highlights the most common symptoms experienced by COVID-19 patients in Africa. Fever emerges as the most prevalent symptom, affecting 42.8% of patients, followed by cough (33.3%), headache (11.3%), and breathing problems (16.8%). These findings align with global patterns of symptomatology associated with COVID-19, reaffirming the consistency of clinical presentations across diverse populations. Moreover, the study

identifies additional, albeit less frequent, symptoms such as diarrhea (7.5%) and rhinorrhea (9.4%), providing valuable insights into the spectrum of clinical manifestations of the virus in African patients. Understanding these diverse symptom profiles is essential for accurate diagnosis, clinical management, and public health interventions.[21]

The reported fatality rate of 5.6% underscores the severity of COVID-19 in Africa and emphasizes the importance of robust healthcare systems and timely interventions to mitigate adverse outcomes. Importantly, the absence of publication bias in the study enhances the reliability and validity of the findings, bolstering confidence in the accuracy of the reported clinical characteristics and outcomes. Overall, this study represents a significant contribution to the growing body of literature on COVID-19, providing the first comprehensive analysis of its clinical characteristics in Africa. By elucidating key aspects of the disease's presentation and progression in this context, the findings inform public health strategies, clinical practice, and future research endeavors aimed at combating the pandemic on the continent.[21]

The phenomenon of breakthrough infections with SARS-CoV-2 in fully vaccinated individuals is under intense investigation to guide ongoing pandemic response and vaccination strategies. Monitoring breakthrough infections presents challenges outside of controlled trials, necessitating both laboratory and observational studies to understand factors influencing vaccine effectiveness against different levels of COVID-19 severity. Rather than isolating specific contributors like age, viral variants, or time since vaccination, breakthrough rates are seen as influenced by the individual's immunity level, the specific viral variant encountered, and the severity of the disease. Key unresolved questions include the transition to endemicity, potential adaptations of vaccines for viral variants, identification of immune protection indicators, and managing breakthrough infections through boosters amid global vaccine supply constraints. Understanding these complexities is crucial for shaping future public health responses to COVID-19.[19]

A study aimed to investigate the incidence and risk factors associated with breakthrough infections in individuals fully vaccinated against COVID-19 in Belgium between February 1, 2021, and December 5, 2021. The research included all persons aged 18 and above who had been fully vaccinated for at least 14 days. Breakthrough infections, defined as laboratory-confirmed SARS-CoV-2 infections occurring after vaccination, were identified, and their incidence was determined. The factors associated with breakthrough infections were analyzed using COX proportional hazard models. The study found that among 8,062,600 fully vaccinated adults, there were 373,070 breakthrough infections, resulting in an incidence rate of 11.2 (95% CI 11.2–11.3) per 100 person-years. Notably, vaccination with Ad26.COV2.S or ChAdOx1 was associated with a higher risk of breakthrough infection compared to BNT162b2 (mRNA Pfizer-BioNTech), while mRNA-1273 (mRNA Moderna) was associated with a lower risk. Additionally, a prior COVID-19 infection was found to be protective against breakthrough infection, as was receiving an mRNA booster. During breakthrough infections, individuals with a prior COVID-19 infection were less likely to experience COVID-19 symptoms compared to those who were naïve to the virus. This finding highlights the protective effect of hybrid immunity, where both natural infection and vaccination contribute to immune protection.[9]

Implications for vaccination strategies

In the field of vaccinology, the primary objective has traditionally centered on reducing the severity of disease upon infection, with the secondary aim of preventing infection altogether. This approach is rooted in the understanding that even if infection occurs, a milder form of the illness can significantly reduce morbidity and mortality rates8. The ultimate challenge in vaccinology lies in the eradication of the targeted pathogen from the human population.[1] Historically, this feat has only been achieved once, with the successful eradication of smallpox through widespread vaccination campaigns.[2] Smallpox stands as a remarkable testament to the power and efficacy of

vaccination when coupled with coordinated global efforts.

However, the landscape shifts with the emergence of novel pathogens like SARS-CoV-2, the virus responsible for COVID-19. Despite remarkable advancements in vaccine development and deployment, complete eradication of SARS-CoV-2 presents formidable challenges. This is primarily due to several factors;

Short-lived Immune Response

Both natural infection and vaccination against SARS-CoV-2 elicit immune responses, but the duration and strength of protection can vary. Evidence suggests that immunity wanes over time, leading to the potential for reinfection or breakthrough infections, albeit typically with milder symptoms. This phenomenon necessitates ongoing vaccination campaigns and booster doses to sustain immunity levels within the population.[4]

Viral Evolution

RNA viruses, such as SARS-CoV-2, possess inherently higher mutation rates compared to DNA viruses. This genetic plasticity enables them to rapidly adapt to selective pressures, including immune responses generated by vaccination or previous infections. Consequently, the emergence of new variants with altered transmissibility, virulence, or antigenic profiles can pose challenges to existing vaccines' effectiveness and immunity conferred by natural infection.[3]

The emergence of breakthrough COVID-19 infections, defined as cases of COVID-19 occurring in individuals who have been fully vaccinated, has raised concerns regarding vaccine efficacy and the impact of emerging variants.[5] These breakthrough infections raise questions regarding the duration and strength of immunity conferred by vaccination, as well as the potential for viral escape from vaccine-induced immunity. Breakthrough infections can occur for various reasons, including waning immunity over time, incomplete vaccine protection, and the presence of new viral variants with altered antigenic properties.[6] While COVID-19 vaccines have demonstrated high efficacy in preventing severe disease and hospitalization, breakthrough infections highlight the need for ongoing monitoring and evaluation of vaccine effectiveness in real-world settings.

The COVID-19 pandemic has left an indelible mark on health, societies, and economies worldwide, with the African region being no exception. As of December 31, 2021, the 47 countries within the WHO African region reported a significant burden of COVID-19, with 7.1 million infections and 155,000 deaths. While these numbers represent 2.5% and 2.9% of the global burden of COVID-19, respectively, they likely underestimate the true extent of the problem due to several factors, including limited testing capacity and underreporting. Moreover, the burden of COVID-19 is not evenly distributed across the region, with wide variations in the number of infections and deaths per 100,000 population among different countries.[10]

The variation in the number of infections within and across countries in Africa can be attributed to socioecological and biophysical factors. Socioecological factors such as population density, age distribution, and hygiene practices influence the rate of transmission of SARS-CoV-2. Public health measures, including lockdowns and adherence to safe hygiene practices, play a crucial role in mitigating the impact of these socioecological factors on transmission rates. On the other hand, biophysical factors, such as the presence of comorbidities like hypertension, diabetes (type 2), chronic obstructive pulmonary disease, HIV, and obesity, contribute to increased severity and risk of mortality following infection. The prevalence of these comorbidities varies across Africa, with some populations experiencing a high burden of multiple conditions.[10]

In response to the challenges posed by the COVID-19 pandemic, health systems across Africa have implemented various strategies to mitigate the effects of biophysical factors. These strategies

include surveillance, effective case management, and the use of available vaccines to enhance antibody development and reduce the severity of the disease. Vaccination campaigns aim to protect vulnerable populations and prevent severe outcomes, particularly among individuals with underlying health conditions.

Understanding the incidence, risk factors and outcomes of severe breakthrough infections is paramount for informing public health interventions and refining vaccination strategies. Factors contributing to breakthrough infections may include host-related factors such as age, underlying health conditions, and immunocompromised status, as well as environmental factors such as exposure to high viral loads or crowded indoor settings.[7]

While numerous studies have investigated breakthrough infections in diverse populations and settings, there remains a paucity of evidence in other African countries. Addressing this knowledge gap is essential for tailoring COVID-19 vaccination programs and optimizing disease control measures in other African countries.

This systematic review aims to synthesize available evidence on breakthrough infections among hospitalized patients in the African region, shedding light on the epidemiology, clinical characteristics, and outcomes of severe breakthrough cases. By consolidating existing data and identifying gaps in knowledge, this review seeks to provide insights into the challenges and opportunities in mitigating the impact of breakthrough infections and optimizing COVID-19 management strategies in Africa.

Objective of the Literature Review

The objective of this literature review is to comprehensively synthesize available evidence on breakthrough COVID-19 infections among hospitalized patients in Africa. Specifically, the review aims to:

a) Investigate the incidence of breakthrough infections among individuals who have been fully vaccinated against COVID-19: This aspect of the review focuses on understanding how frequently breakthrough COVID-19 infections occur among individuals who have completed their vaccination regimen. The investigation begins with a review of regional data then followed by country data. By examining available data, the review aims to quantify the proportion of vaccinated individuals who still contract the virus and develop symptomatic or asymptomatic infections necessitating hospitalization.

b) Identify the risk factors associated with severe breakthrough infections, including demographic, clinical, and environmental factors: Beyond simply identifying the occurrence of breakthrough infections, this objective delves deeper into the factors that may increase the likelihood of severe disease among vaccinated individuals. These risk factors could include demographic characteristics (such as age, gender, and underlying health conditions), clinical factors (such as vaccine type, time since vaccination, and immune status), and environmental factors (such as exposure to high viral loads or crowded settings). Understanding these risk factors is crucial for targeting interventions and allocating resources effectively to prevent severe breakthrough infections.

c) Examine the outcomes of severe breakthrough infections, including hospitalization rates, disease severity, and mortality among hospitalized patients: This aspect of the review focuses on understanding the clinical course and outcomes of breakthrough infections among hospitalized patients. It involves assessing metrics such as hospitalization rates, disease severity (e.g., need for intensive care, mechanical ventilation), length of hospital stay, and mortality rates among vaccinated individuals who develop severe COVID-19. By examining these outcomes, the review aims to provide insights into the impact of breakthrough infections on the healthcare system and the prognosis of affected individuals.

d) Address the knowledge gap regarding breakthrough infections in other African countries and contribute to the understanding of COVID-19 epidemiology and vaccine effectiveness in the region: Despite extensive research on COVID-19

worldwide, there may be limited data available specifically pertaining to breakthrough infections in Africa. Therefore, this objective aims to fill this knowledge gap by synthesizing existing evidence from studies conducted within the African context. By focusing on local epidemiology and vaccine effectiveness, the review provides insights that are directly relevant to public health policymakers, healthcare practitioners, and researchers in Africa.

e) Provide insights into public health interventions and vaccination strategies tailored to mitigate the impact of breakthrough infections and optimize COVID-19 management in Africa: Ultimately, the overarching goal of the literature review is to translate its findings into actionable recommendations for public health interventions and vaccination strategies in Africa. By identifying risk factors, understanding outcomes, and addressing knowledge gaps, the review can inform the development of evidence-based policies and practices aimed at mitigating the impact of breakthrough infections, optimizing COVID-19 management, and improving vaccine uptake and distribution.

Materials and Methods

This systematic review adhered to the guidelines outlined in the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) Statement.13 Institutional Review Board approval was deemed unnecessary for this study.

A comprehensive literature search was undertaken to identify outcome studies pertaining to the incidence, risk factors, and outcomes of severe breakthrough COVID-19 infections among hospitalized patients in Africa. The search spanned from 2021 to 12 April 2024 to ensure inclusivity of relevant studies. Major academic databases including PubMed, Google Scholar, and Scopus were meticulously searched using appropriate keywords and Boolean operators to optimize search results.

The screening process involved evaluating titles, abstracts, and full texts of the retrieved articles to determine their relevance to the research question. Studies that did not meet the predefined criteria were excluded, while those meeting the criteria were included for detailed analysis. Additionally, reference lists of relevant articles were manually scanned to identify any additional studies that may have been missed during the initial search process.

Through this rigorous screening process, a final selection of relevant studies was compiled for thorough review and synthesis. The selected studies provided valuable information into the incidence, risk factors, and outcomes of severe breakthrough COVID-19 infections among hospitalized patients in Africa. The synthesized findings from these studies would contribute significantly to understanding the burden and clinical characteristics of breakthrough infections in the region, thereby informing evidence-based interventions and healthcare policies aimed at mitigating the impact of COVID-19.

Inclusion criteria

1. Study Design

- Observational studies (e.g., cohort studies, case-control studies) and clinical trials reporting breakthrough COVID-19 infections among hospitalized patients in Africa.
- Studies published in peer-reviewed journals or preprint repositories.
- Studies with a defined study population and clear methodology for identifying breakthrough infections.

2. Population

- Hospitalized patients in Africa who have tested positive for COVID-19 after completing the recommended vaccination regimen.
- Patients of all ages, genders, and comorbidities.

3. Outcome Measures

- Incidence of breakthrough COVID-19 infections among vaccinated hospitalized patients.

- Risk factors associated with severe breakthrough infections, including demographic, clinical, and environmental factors.
- Clinical outcomes of breakthrough infections, such as hospitalization rates, disease severity, need for intensive care, mechanical ventilation, length of hospital stay, and mortality rates.

4. Timeframe

- Studies published between2021to 12 April 2024 to capture relevant data on breakthrough infections during the COVID-19 pandemic.

Exclusion criteria

1. Study Design

- Editorials, commentaries, letters, opinion pieces, and reviews without original data.
- Studies lacking clear methodology or insufficient detail on breakthrough infections among hospitalized patients.

2. Population

- Studies conducted outside of Africa or with a study population that is not exclusively hospitalized patients.

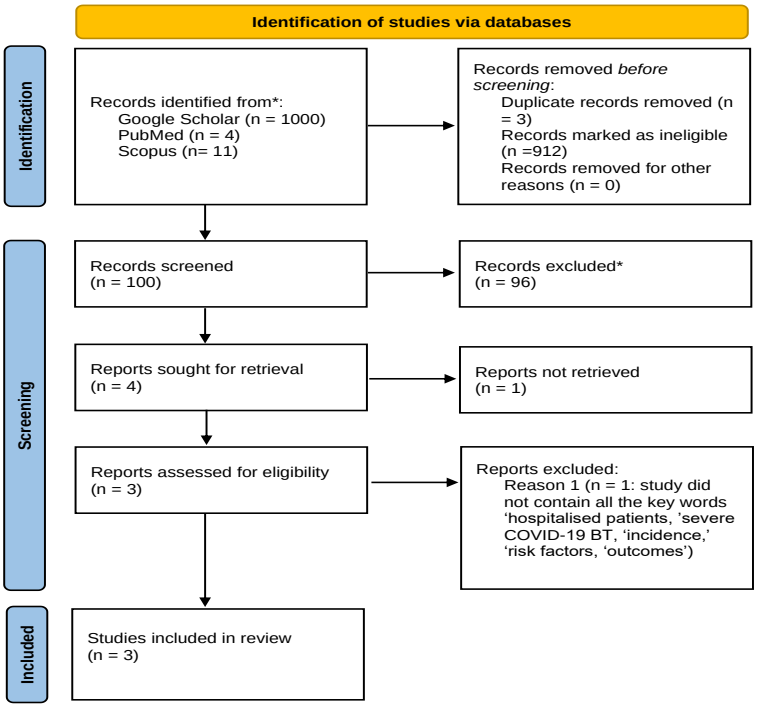
3. Outcome Measures

- Studies reporting breakthrough infections but lacking data on hospitalization status or clinical outcomes.
- Studies with incomplete or inconsistent reporting of outcomes, making it difficult to assess the severity of breakthrough infections.

4. Language

- Studies published in languages other than English, as resources for translation may be limited.

PRISMA 2009 Flow Diagram



Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

Results

A systematic literature search was conducted across three major academic databases, PubMed, Google Scholar, and Scopus, to identify relevant studies focusing on severe breakthrough COVID-19 infections among hospitalized patients in

Africa. The search encompassed articles published from2021 to 12 April 2024, ensuring the inclusion of recent literature pertinent to the research question. The search strategy incorporated key terms such as "incidence," "risk factors," "outcomes," and "severe COVID-19 breakthrough infections among hospitalized patients in Africa" to comprehensively capture relevant studies.

The search yielded a total of 1015 results across all databases, with PubMed returning 4 results, Google Scholar providing 1000 results, and Scopus generating 11 results. After removing duplicates, 100 unique results remained for further evaluation. From this pool of unique results, 97 articles were excluded during the screening process as they did not meet the predefined inclusion criteria, which focused on studies investigating severe breakthrough COVID-19 infections among hospitalized patients in Africa.

The inclusion criteria were carefully established to ensure that only relevant studies were considered for inclusion in the synthesis. Following the application of the inclusion criteria, 3 studies were deemed eligible for inclusion in the synthesis. These studies, conducted inEgypt, South Africa, and one systematic review, provided valuable insights into the incidence, risk factors, and outcomes of severe breakthrough COVID-19 infections among hospitalized patients in Africa, contributing to a comprehensive understanding of the challenges posed by breakthrough infections in the region.

In Egypt, a comprehensive study examined the clinical features and risk factors associated with breakthrough infections among hospitalized patients. Younger age groups, males, and recipients of inactivated vaccines showed higher rates of breakthrough infections, while those who received mRNA vaccines had lower rates. Breakthrough cases tended to have shorter hospital stays and lower fatality rates compared to unvaccinated individuals. However, significant risk factors for breakthrough infections (VBT) included younger age, male gender, and receipt of inactivated vaccines. Data were collected from the severe acute respiratory infections surveillance database spanning from September 2021 to April 2022, including information on SARS-CoV-2 confirmed patients hospitalized in 16 hospitals. Demographic characteristics, clinical presentation, and outcomes of patients were analyzed descriptively. Patients with VBT were compared to those not fully vaccinated (UPV). Bivariate and multivariate analyses were conducted using Epi Info7 software to identify risk factors associated with VBT. A total of 1,297 patients were included in the analysis, with a mean age of 56.7 years and a male predominance of 41.5%. The majority received inactivated vaccines (64.7%), followed by viral vectors (25%) and mRNA vaccines (7.7%). VBT was identified in 156 patients (12.0%), showing an increasing trend over time. VBT was significantly higher among younger age groups (16-35 years), males, and those who received inactivated vaccines compared to UPV. Conversely, receiving mRNA vaccines was associated with significantly lower VBT rates. Patients with VBT tended to have shorter hospital stays and lower case fatality rates compared to UPV. Multivariate analysis identified younger age, male gender, and receipt of inactivated vaccines as significant risk factors for VBT.[15]

Meanwhile, a study in South Africa delved into the hospitalization patterns and reinfection rates among healthcare workers across various phases of the COVID-19 pandemic, focusing on the beta, delta, and omicron variants. Notably, the median length of hospital stay exhibited a significant shift over time. During the beta and delta periods, the median hospital stay stood at 5 days, while it decreased to 3 days during the omicron period. This reduction in hospitalization duration was statistically significant ($p<0.0001$), implying improved outcomes or management strategies during the omicron surge.[11]

Moreover, the investigation highlighted reinfection dynamics among healthcare workers. Despite the dominance of the omicron variant

during the study period, a small proportion had previous infections with the beta or delta variants. Specifically, 0.16% and 4.5% of healthcare workers infected during the omicron period had been previously infected with the beta and delta variants, respectively. This suggests either partial cross-protection from previous infections or the possibility of reinfection with earlier variants due to temporal proximity. Interestingly, analyses of baseline characteristics such as age, sex, and comorbidities revealed no significant differences between healthcare workers reinfected during the omicron period and those initially infected during the beta and delta periods.[11]

Lastly, the reviewed studies of the systematic review that aimed to assess the existing evidence on BTIs of SARS-CoV-2, provide a detailed breakdown of the variant distribution and clinical characteristics associated with breakthrough COVID-19 infections (BTIs). Among the reported BTIs, the Delta variant (B.1.617.2) accounted for the vast majority, constituting 96% of cases, indicating its predominance in breakthrough infections. Other variants contributing to BTIs included the Alpha variant (B.1.1.7), Gamma (P.1), Beta (B.1.351), Kappa (B.1.617.1), and Iota (B.1.526), among others. Notably, a subset of BTIs was associated with variants such as Epsilon (B.1.427/B.1.429) and Mu (B.1.621), underscoring the diverse viral strains contributing to breakthrough infections.[12]

Furthermore, the analysis highlights the prevalence of pre-existing comorbidities among patients with BTIs, with 8.4% of individuals having underlying health conditions such as chronic bronchitis, obesity, dyslipidemia, type 2 diabetes mellitus, and immunosuppressive conditions. Additionally, a significant proportion of reported BTIs occurred in healthcare workers (HCWs), comprising 2.3% of cases, indicating the occupational risk faced by frontline healthcare personnel.[12]

The clinical presentation of BTIs ranged from asymptomatic cases to severe pneumonia, with some patients requiring admission to intensive care units (ICUs) and mechanical ventilation. While the majority of patients recovered without complications, a notable portion necessitated hospitalization for oxygen supplementation, intubation, or extracorporeal membrane oxygenation (ECMO). Tragically, a small percentage of patients succumbed to the infection, with 0.6% experiencing fatal outcomes.[12]

The combined analysis of these studies provides specific findings into the epidemiology, risk factors, and clinical features of severe breakthrough COVID-19 infections among hospitalized patients in Africa. Across diverse geographic regions and study designs, several consistent findings emerged, aiding in a comprehensive understanding of the challenges posed by breakthrough infections and guiding evidence-based interventions and healthcare strategies tailored to local contexts.

Regarding epidemiology, the studies revealed a concerning incidence of breakthrough infections among vaccinated individuals, highlighting ongoing transmission risks within vaccinated populations. Specifically, the Tunisia study demonstrated a high incidence rate of breakthrough infections, emphasizing the persistent threat despite vaccination efforts. Similarly, the South Africa study noted a substantial increase in breakthrough infections, particularly during the Omicron period, suggesting evolving dynamics of infection spread.

Risk factors associated with severe breakthrough infections were identified across studies, aiding in risk stratification and targeted interventions. Younger age emerged as a consistent risk factor, as evidenced by findings from the Egypt study, which highlighted higher rates of breakthrough infections among younger age groups. Additionally, incomplete vaccination schemas and specific vaccine types, such as inactivated vaccines, were associated with increased risk, as observed in both the Tunisia and Egypt studies.

Clinical characteristics of breakthrough infections were elucidated, informing healthcare strategies for managing severe cases. The studies consistently reported a notable proportion of severe or critical cases among breakthrough infections, underscoring the importance of continued vigilance and adherence to preventive measures. Notably, the South Africa study revealed variations in the severity of breakthrough infections across different SARS-CoV-2 variant periods, with the Omicron variant associated with lower severity compared to previous variants.

By synthesizing evidence from diverse settings, the synthesis provides actionable findings for informing evidence-based interventions and healthcare strategies. These findings include the need for ongoing surveillance and risk stratification to identify vulnerable populations, tailored vaccination strategies to address evolving epidemiological dynamics and vaccine efficacy, and the importance of maintaining preventive measures despite vaccination efforts to mitigate the impact of breakthrough infections.

The synthesis offers specific and actionable findings into severe breakthrough COVID-19 infections among hospitalized patients in Africa, facilitating targeted interventions and healthcare strategies to address the challenges posed by breakthrough infections in diverse local contexts.

Discussion

This study conducted in Egypt aimed to provide a thorough understanding of COVID-19 vaccine breakthrough infections (VBT) among hospitalized patients, focusing on clinical features, risk factors, time trends, and outcomes. The findings revealed a concerning upward trend in VBT, with 156 cases identified among the 1,297 patients analyzed, indicating an overall prevalence of 12.0%. This trend was particularly notable among younger males and individuals who had received inactivated vaccines, with younger age groups (16-35 years) exhibiting significantly higher rates of VBT compared to other age cohorts.

Conversely, recipients of mRNA vaccines exhibited lower rates of VBT. Among the patients analyzed, the majority received inactivated vaccines (64.7%), followed by viral vector vaccines (25%) and mRNA vaccines (7.7%). Despite the occurrence of breakthrough infections, patients with VBT tended to experience shorter hospital stays and lower fatality rates compared to their unvaccinated counterparts. However, it's essential to note that breakthrough infections still pose a risk, albeit with less severe outcomes compared to unvaccinated cases.

Through multivariate analysis, the study identified several key risk factors associated with VBT. Younger age emerged as a significant risk factor, with the age group of 16-35 years showing the highest prevalence of VBT. Additionally, being male was associated with an increased likelihood of VBT, indicating potential gender-based differences in vaccine efficacy or immune response. Notably, receipt of inactivated vaccines was identified as a significant risk factor, with recipients of these vaccines exhibiting higher rates of breakthrough infections compared to those who received other vaccine types.

These findings have important implications for vaccination strategies and public health measures. Understanding the factors contributing to VBT allows for targeted interventions to mitigate risks and enhance vaccine effectiveness. Strategies such as booster doses or prioritizing certain vaccine types for specific demographics may help address the rising trend of breakthrough infections, particularly among high-risk groups like younger males.

Overall, this comprehensive study sheds light on the evolving landscape of COVID-19 vaccine breakthrough infections in Egypt, providing valuable insights for policymakers, healthcare professionals, and the broader scientific community. Continued monitoring and research

are essential to adapt vaccination strategies and effectively manage the ongoing threat of COVID-19.[15]

South Africa

In a study conducted among healthcare workers in Sisonke, South Africa, the researchers aimed to assess breakthrough COVID-19 infections during periods characterized by the circulation of the Beta, Delta, and Omicron variants of concern. The study examined several key aspects of breakthrough infections, including their incidence, hospitalization trends, age distribution among infected healthcare workers, severity of infections, and clinical outcomes. Results from the study revealed a total of 40,538 breakthrough COVID-19 infections observed throughout the study period, with varying numbers recorded during periods dominated by the Beta, Delta, and Omicron variants. Particularly noteworthy was the substantial increase in daily infections observed during the Omicron period, which was three times higher than the peak observed during the Delta variant period.[11]

Analysis of hospitalization trends during the study period revealed a significant departure from previous patterns, particularly during the Omicron period. Unlike the Delta period, the Omicron period exhibited an early and clear separation of hospitalizations from the percentage of cases, suggesting that a greater proportion of cases during the Omicron period did not require hospitalization compared to previous variants. Furthermore, the study highlighted differences in the age distribution of infected healthcare workers across different variant periods. Specifically, the Omicron variant affected a higher proportion of healthcare workers in the 18–30-year age group compared to older age groups, indicating potential variations in susceptibility or exposure among different demographic groups during the Omicron period.[11]

Regarding the severity of breakthrough infections, the study reported a total of 1,914 breakthrough-related hospitalizations, with varying proportions observed across the Beta, Delta, and Omicron periods. Notably, during the Omicron period, a higher percentage of hospitalized healthcare workers required general ward care, with fewer requiring high care or intensive care compared to previous periods. Clinical outcomes among hospitalized healthcare workers also varied across different variant periods. During the Beta and Delta periods, a greater proportion of hospitalized individuals required supplementary oxygen and ventilation compared to the Omicron period. Additionally, the median length of hospitalization was significantly shorter during the Omicron period compared to previous variants.[11]

The study among healthcare workers in South Africa highlighted a substantial increase in breakthrough infections during the Omicron period. It noted differences in hospitalization trends and age distribution among infected healthcare workers across variant periods. Importantly, while breakthrough infections were more common during the Omicron period, the severity of illness associated with these infections was lower compared to previous periods dominated by dominated by the Beta and Delta variants. Possible explanations for this trend include high population SARS-CoV-2 seroprevalence, waning vaccine effectiveness over time, increased infectivity of the Omicron variant, immune evasion by Omicron, or a combination of these factors.

Systematic review on COVID breakthrough infections

A systematic review of the characteristics of COVID-19 breakthrough infections among vaccinated individuals and associated risk factors' findings emphasize several critical points regarding breakthrough COVID-19 infections (BTIs) and the need for standardized surveillance protocols to assess their nature and burden effectively. Firstly, the study indicates that BTIs are not necessarily indicative of selection towards specific immunity-evading variants but rather reflect the prevalence of circulating variants within the community. This underscores the

importance of standardized surveillance reporting protocols to accurately gauge the burden of reinfections among vaccinated individuals.[12]

Moreover, the review suggests that studies on BTIs can provide findings into the neutralizing response to SARS-CoV-2 infection and corresponding immunity. However, the absence of systematic genomic sequencing of positive cases globally hinders advancements in public health surveillance to manage the pandemic effectively at both individual and collective levels. Therefore, further investigations, including genetic comparisons of SARS-CoV-2 strains, are necessary to understand the frequency and pathophysiology of reinfections comprehensively. Despite the proven efficacy of COVID-19 vaccines, the possibility of BTIs remains a reality, particularly with the emergence of variants of concern. Various factors contribute to BTIs, including the transmission dynamics of SARS-CoV-2 variants, individual behavioral characteristics, and vaccination status.[12]

The systematic review identified various factors contributing to breakthrough COVID-19 infections (BTIs) among vaccinated individuals. It emphasized the need for standardized surveillance protocols to assess the nature and burden of BTIs effectively. Importantly, the review highlighted the reality of BTIs, particularly with the emergence of variants of concern, and underscored the importance of continued research and surveillance to understand and mitigate their impact on public health.

Conclusion

The findings from the studies conducted in South Africa and Egypt, collectively highlight the persistent challenges posed by breakthrough COVID-19 infections despite widespread vaccination efforts. These studies emphasize the importance of sustained vigilance and proactive public health interventions to navigate the complexities surrounding breakthrough infections amid the evolving landscape of the pandemic.

Key takeaways from these studies include the identification of various risk factors associated with breakthrough infections, such as age, gender, and vaccination status. Understanding these risk factors is crucial for implementing targeted strategies aimed at reducing the incidence and severity of breakthrough infections among vaccinated individuals. For example, younger age groups and males were found to be at higher risk of breakthrough infections in some studies, underscoring the importance of tailored interventions for specific demographic groups.

Moreover, the emergence of variants of concern, such as the Omicron variant, adds another layer of complexity to breakthrough infections. These variants may impact vaccine effectiveness and breakthrough infection rates differently. Hence, ongoing monitoring and surveillance efforts are essential to assess the spread and impact of variants and inform adjustments to vaccination strategies and public health measures accordingly.

The findings underscore the dynamic nature of the COVID-19 pandemic and the importance of adapting strategies in response to emerging challenges. Ramping up vaccination efforts, particularly targeting high-risk populations and healthcare workers, is imperative to curb the incidence of breakthrough infections and mitigate their consequences. Expanding vaccine coverage and ensuring accessibility are critical steps in bolstering community immunity and reducing the risk of severe outcomes associated with breakthrough infections.

Establishing robust surveillance systems to monitor breakthrough infections and track variant dynamics is essential. Standardized reporting protocols and genomic sequencing capabilities are crucial for accurately assessing the prevalence of variants and evaluating their impact on vaccine effectiveness. By enhancing surveillance, we can promptly detect emerging threats and tailor public health responses accordingly. Despite vaccination, adherence to non-pharmaceutical interventions remains vital in reducing the risk of

breakthrough infections, especially in areas with high transmission rates or emerging variants. Emphasizing the importance of mask-wearing, physical distancing, and hand hygiene can help mitigate the spread of COVID-19 and protect vulnerable populations from infection.

Continued research is needed to deepen our understanding of the mechanisms underlying breakthrough infections and identify additional risk factors. Longitudinal studies and clinical trials can provide valuable insights into the duration of vaccine-induced immunity, the efficacy of booster doses, and the effectiveness of updated vaccines against emerging variants. Generating local data through similar studies in other African countries is essential to tailor vaccination strategies and public health interventions to the local context, ultimately improving our ability to control the spread of COVID-19 and protect the population from severe illness.

Limitations

One potential limitation of the synthesis is the scarcity of available studies conducted in Africa, as evidenced by the small number of published studies eligible for inclusion. This limitation may have impacted the breadth and depth of the evidence synthesized, potentially limiting the comprehensiveness of the findings. The limited number of studies may reflect gaps in research funding, or prioritization of research on breakthrough infections in Africa, which could hinder the ability to draw robust conclusions about the epidemiology, risk factors, and outcomes of breakthrough infections in the region. Consequently, the findings of the synthesis may not fully capture the diversity and nuances of breakthrough infections in Africa, highlighting the need for additional research to address knowledge gaps and enhance understanding of the phenomenon in the local context.

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