Low COVID-19 impact in Africa: The multifactorial Nexus

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Abstract
Africa has defied predictions of being the worst hit by the novel coronavirus disease (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, which has devastated Europe, the Americas, and some Asian countries. However, with a current second and third wave of the COVID-19 pandemic across other continents, pertinent questions have arisen regarding the lower disease severity and seemingly better outcomes in most African countries. Several factors have been proposed as discussed in this review including, underreporting, quick lockdown measures, effective public health intervention, younger population structure, cross-immunity and experience from fighting previous epidemics, such as the Ebola virus outbreak, previous infections or vaccinations, genetic predisposition, and tropical climate. We have discussed the implications of these factors on the magnitude of the outbreak and the better-than-expected outcomes observed in Africa. In addition, other potential factors like vitamin-D deficiency and chronic non-communicable diseases could predispose non-African regions to severe COVID-19 outcome. Therefore, this review further advocates for research to understand the precise mechanisms responsible for the pandemic's relatively mild impact in Africa and proposed recommendations to prevent an infection surge.

Keywords
COVID-19, SARS-CoV-2, Africa, lower severity, key factors
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Introduction
Coronavirus Disease 2019 (COVID-19), caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has been relatively mild in Africa compared to other regions of the world (Bamgboye et al., 2021). This disease manifestation pattern and outcome in Africa has generated interest in the possible roles of immune responses and other underlying factors in COVID-19 pathogenesis (Ovsyannikova et al., 2020). Given the poor socio-economic determinants allowing vulnerability to public health threats such as Lassa fever and malaria, initial predictions were towards a more devastating impact in Africa, including higher SARS-CoV-2 infection burden and COVID-19-related mortality. This has not been the case, likely due to the quick responses of most African governments. Africa is currently the second least affected continent and has reported approximately 3% and 3.7% of the global cases and associated deaths, respectively (Africa CDC, 2021). Although COVID-19 transmission continues to increase on the continent, most outcomes have been manageable, despite the weakened and overstretched health care systems. Approximately 90% of overall infected patients recover (Getachew, 2021); meanwhile, about 80% of the infections are asymptomatic (Chakamba, 2020; WHO, 2020b), and this has baffled researchers across the globe. The low case and death reports may indicate a low impact of the COVID-19 pandemic on Africa or may probably be due to underreporting. Despite this, mortality in critically ill patients in Africa is higher than has been observed in Europe, Asia, North America and South America (Africa CDC, 2021). Therefore, in this review, we elucidate proposed factors contributing to seemingly less severe COVID-19 outcomes in Africa and recommended more research to better understand SARS-CoV-2 infection mechanisms on the continent.

1. Underreporting
According to the Africa Centre for Disease Control and Prevention, 4,843,874 COVID-19 cases and 130,814 deaths, with a case fatality ratio of 2.7%, have been reported in the 55 African Union Member States as of June 1, 2021 (Africa CDC, 2021). More than one-third of the confirmed cases and deaths are from South Africa, which may be attributed to increased testing. Moreover, surveys from some African countries show a substantially higher proportion of individuals with SARS-CoV-2 antibodies than the officially reported case counts (Chibwana et al., 2020; Quashie et al., 2021). So far, Africa has conducted the lowest tests per capita due to testing costs, availability of appropriate facilities, political will and the population perception about the pandemic (Fouogue et al., 2020; Lee et al., 2020; Lowe, 2020). Botswana has performed the most tests on the continent, recording 498,088 tests per million compared to 1,120,150 and 1,788,480 tests per million in Italy and the United Kingdom (UK), respectively (Worldometer, 2021).

Altogether, reduced testing may be contributing to the low numbers of COVID-19 cases reported on the continent, given that there seem to be more cases in African countries with higher testing rates, such as South Africa and Morocco (Figure 1). Additionally, the reported deaths are also low compared to the global counts; however, considering the reportedly low case reports, the death counts seem disproportionately high. This is reflected in the case mortality reported on the continent (Africa CDC, 2021), which may also border on underreporting due to reduced active community testing. Most African countries have increased their testing capacities, but there is still room for improvement compared to countries like the UK and Italy.

2. Quick lockdown measures by African Governments to reduce transmissions
Following the declaration of COVID-19 as a pandemic by the WHO on March 11, 2020, most African governments’ response to the pandemic was quick, decisive and drastic, at a great economic cost (Haider et al., 2020; Ogunleye et al., 2020). Globally, lockdown interventions have championed the effective suppression of the spread of SARS-CoV-2 (Islam et al., 2020). Although all African countries responded differently to the pandemic, 34 out of the 54 countries introduced lockdowns or curfews at some point and implemented control measures such as airport screenings or closure, avoiding handshakes, frequent handwashing, social distancing, and the wearing of face masks (Aloui-Zarrouk et al., 2020). The swift government interventions of imposing lockdown measures, though strenuous and challenging, provided necessary protection to the African population at the most critical time. These proactive and strategic measures have been instrumental in slowing SARS-CoV-2 spread and keeping the number of COVID-19 cases low on the continent. In addition, it allowed hospitals and health workers to better prepare with different treatment methods and postponed the pandemic’s proposed worst outcome.

Increased SARS-CoV-2 spread may likely result in greater disease severity due to the possibility of mutations and the emergence of new variants. This is evident in a country like South Africa, which had the highest COVID-19 burden on the continent and one of the first to report a new SARS-CoV-2 variant, the Beta variant (B.1.351). In some high-income countries where swift lockdown measures were observed, high mortality and variant evolution were mainly observed among the vulnerable and socially disenfranchised populations (Shim et al., 2020).

Also, there have been different responses since the WHO recommended wearing nose masks. Notably, many African governments have implemented this measure, which is suggested to reduce the number of transmitted virus particles (WHO Africa, 2020a). A survey conducted in 18 African countries showed that approximately 85% of public support was for safety measures, including wearing face masks (PERC, 2020). In contrast, many European and North American countries lowered implementation of masking, which may have contributed to the surge in cases reported in these countries. Instituting widespread COVID-19 safety measures appear to have had a protective impact in Africa. Most African countries have weak health infrastructures, with the average intensive care unit (ICU) bed capacity ranging from 2 per 100,000 to 6.5 per 100,000, compared to 34.7 per 100,000 beds for the US population (Craig et al., 2020).
Since the initial strict measures, most African countries have eased most strict measures and reopened some borders, but with control measures to curtail transmission (Tih, 2020). However, since reopening, the number of reported cases has increased in many countries (The Conversation, 2020); many academics, researchers, politicians and policymakers have expressed views on the challenges of making critical decisions in a situation of many uncertainties (Rijs & Fenter, 2020).

3. Effective public health response due to experience from previous epidemics
Though initial training on management of the pandemic was given by the African Centre for Disease Control (CDC) and WHO to frontline health workers (Africa CDC, 2020), Africa already had decades of experience tackling infectious disease outbreaks and epidemics (Arias et al., 2016; Omoleke et al., 2018). Several African countries had battled, or prepared for, the Ebola outbreak. As such public health measures, including isolating infected persons, contact tracing and quarantine standard operating procedures (SOPs) developed for Ebola, could be co-opted to mitigate COVID-19 impact (Endomba et al., 2020). Other countries had human and logistic capacities related to the polio eradication programme. Existing outbreak mitigation expertise in African countries (Ilesanmi & Afolabi, 2021) was crucial and may have effectively limited viral importations and spread. Thus, while many African countries lacked highly developed hospital infrastructures, the existing facilities had evolved resilience and were able to adapt to this new scourge quickly. Africa’s swift response to the pandemic provided valuable time for building public health systems to trace and prevent new cases.

Additionally, traditional medical practices and the use of herbs in treating most diseases are prevalent in Africa (Mahomoodally, 2013). Herbs enhance the immune system and place the human body in a healthier position to fight infections (Rawat et al., 2020). Though largely unverified, natural remedies have been speculated to have helped curtail the severity of SARS-CoV-2 in Africa. When combined with orthodox treatment, traditional Chinese medicines have been shown to have a positive outcome for COVID-19 (Li et al., 2020). Still controversial, the use of herbal medicine is prevalent in Africa (Anochie et al., 2018; James et al., 2018) and may have contributed to the reduced impact of COVID-19 in Africa. Many people used medicinal plants during the exponential infection phase, but it is unknown if any of these were useful (Nkeck et al., 2020). Some herbs have been reported to enhance the immune system to fight infections (Mills et al., 2005), improving COVID-19 patients’ symptoms, inflammation, respiratory difficulties, enhanced pulmonary infiltration absorption and quality of life (Li et al., 2020; Rawat et al., 2020). Hence, more research on these claims is needed to determine if herbal preparations have played any role in COVID-19 mitigation.

4. Younger population
Human immune function declines with age (Yung, 2000), while infectious disease and primary T-cell defect-associated morbidities increase with age (Jiang et al., 2013). Therefore, Africa’s young population-age structure, with a median age of 19.7 years and 60% of the population < 25 years, could have mediated the low COVID-19 severity on the continent. The younger population have a disproportionately lower chronic disease burden (Gore et al., 2011), and the severity of respiratory virus-mediated infections is often age-dependent (Galanti et al., 2019). Increasing evidence on SARS-CoV-2 infection reveals that older individuals (>60 years) are more susceptible to a more severe disease outcome (Davies et al., 2020). In line with this, some studies have reported that expression of ACEII receptor, which the virus uses to invade host cells, decreases with age (Chen et al., 2020a; Xudong et al., 2006), while others have demonstrated increased expression in respiratory tissues with increasing age (Andrew Baker et al., 2020; Bunyavanich et al., 2020). This may explain why older people are more likely to be infected than younger individuals with the same risk factors. About 3% of Africans fall in this category compared with 19 % in Europe, 17% in the US and 9% in Asia (Figure 2).

More than 80% of the population in Africa are below 40 years (Figure 3), implying that most COVID-19 cases in Africa are...
asymptomatic and in the younger population. This may also explain the low case reports, which seem to border on underreporting. On the other hand, the asymptomatic presentation could result from a more robust immune system function in younger individuals (Garcia de Jesús, 2020). Hence, understanding the underlying mechanisms of a lower immune function with ageing may improve our competence in preventing and treating infectious diseases like SARS-CoV-2 in the elderly.

5. Multiple previous infections by a wide diversity of infectious agents and Hyper vaccinations

Africa, particularly the tropics, is burdened with numerous diseases, including several neglected tropical diseases (NTDs) (Moeti, 2018). Most of the NTDs are inflammatory (Feasey et al., 2010); this may have primed the immune system of most Africans to other infectious agents. Thus, a heightened immune response triggered by SARS-CoV-2 invasion may potentially quickly eliminate the virus due to a hyperactive immune response. Also, an average African child receives at least six shots of different vaccines before the age of five, including polio, measles, and yellow fever vaccines, with some of these vaccinations repeated during a general vaccination initiative (Shah et al., 2017; Vaccine-Preventable Diseases Programme WHO, 2010). The vaccinations given at birth in most African countries confer broad protection against other infectious diseases and could be protecting Africans from severe COVID-19 outcome (Shah et al., 2017). The exposures to multiple infectious agents and vaccinations may build some level of cross-immunity against infections like the SARS-CoV-2. Cross-reactive antibodies to the virus could be imparted by previous infections, especially with other human coronaviruses (Davies et al., 2020), suggesting a considerable amount of cross-reactivity and host-immune recognition between
different pathogens (Iesa et al., 2020; Panda et al., 2020; Parodi & Cozzani, 2020). Therefore, pre-existing protection may exist in the African population due to naturally acquired infections from previous exposure to other pathogens like influenza, P. falciparum and other coronaviruses (Panda et al., 2020; Tso et al., 2020).

Similarly, a correlation was observed between universal BCG vaccination and COVID-19 mortality (Miller et al., 2020), but not with morbidity (Weng et al., 2020), revealing that BCG vaccinated individuals were less likely to die from COVID-19 disease (Escobar et al., 2020). However, the evidence is still not clear-cut, seeing that BCG vaccination was widespread in Europe until the 1900s, and still in use in the UK as of 2018 for at-risk groups (Oxford Vaccine Group, 2020).

6. Genetic Predisposition

A favourable genetic background may also mediate lower COVID-19 severity on the continent (Zeberg & Pääbo, 2020). Researchers have discovered a genetic susceptibility locus with a cluster of six genes on chromosome 3, linked with severe COVID-19 (The Severe COVID-19 GWAS Group, 2020). The genetic variants are Neanderthal-derived, with an estimated 3% prevalence in the African population genome (Price, 2020) and high linkage disequilibrium in non-African populations (Zeberg & Pääbo, 2020). The core ‘risk’ haplotype allele frequency is 4%, 8%, and 30% in admixed Americans, Europeans, and South Asians, respectively, while at least a copy of the risk variant is present in 9%, 16% and 50% of the above populations, respectively (Zeberg & Pääbo, 2020).

The Neanderthal-derived gene is proposed to have devastating effects on the progression of SARS-CoV-2 infection (Zeberg & Pääbo, 2020). This may be specifically associated with the 45,859,651–45,909,024 (hg19) genetic variants on chromosome 3 linked to severe COVID-19 outcome since the recently identified distinct African Neanderthal haplotypes are enriched in immune function and ultraviolet-radiation sensitive genes (Chen et al., 2020b). Thus, the presentation of less COVID-19 severity in Africa could result from the positive selection of the Neanderthal immune booster (Mendez et al., 2013) and ultraviolet protective genes or the lower linkage disequilibrium of the derived genetic variants less significantly associated in the African population. Also, the Neanderthal specific characteristics that bequeath a risk for COVID-19 severity is unknown. Therefore, studies to determine this Neanderthal feature is essential to understanding host genome and pathogenic interaction in COVID-19 patients in Africa and non-African populations.

The second genetic susceptibility locus is on chromosome 9 and is linked to the ABO blood group system (Zhao et al., 2020). A protective effect for COVID-19 severity was observed for blood group O individuals and a higher risk for blood group A than other blood groups (Zhao et al., 2020). Africans have a low prevalence of group A blood type and a higher prevalence of group O blood type (Goel et al., 2021), which provides a selective advantage against infectious diseases. Thus, the pattern of group O prevalence may explain the lower COVID-19 severity in Africa. Also, the von Willebrand factor (VWF), which is significantly lower in blood group O than the other ABO blood groups (Sukhu et al., 2003), could be one of the biological mechanisms involved in COVID-19 severity. This is because the VWF plasma levels, essential in hemostasis (Randi & Laffan, 2016), including stabilising coagulation factor VIII and mediating platelet adhesion, vary according to the ABO blood type (Franchini et al., 2014). Notably, iron homeostasis have been significantly associated with COVID-19 severity (Zhou et al., 2020).

7. Favourable tropical climate

Temperature and humidity variations are the main seasonality drivers that modulate host intrinsic, innate, and adaptive immune responses to viral infections (Moriyama et al., 2020). And a significant decrease in COVID-19 severity and mortality have been associated with a higher temperature, latitude and humidity (Kifer et al., 2020; Sajadi et al., 2020). Tropical weather conditions are associated with less severe SARS-CoV-2 infections, as seen in Africa (Choma et al., 2020; Deyal et al., 2020). However, this is unlike India, which has experienced severe COVID-19 impact (Kujur & Goswami, 2020). India has a high prevalence of obesity (Ranjan et al., 2020), which is a known COVID-19 risk factor (Simonet, 2020); thus, the pangs of the pandemic have been attributed to this underlying factor (Gao et al., 2020; Lichter et al., 2020; Mohammad et al., 2021).

Low temperature with colder and drier air masses seems to favour virus spread, as observed in the US, China, Iran, Italy, South Korea, and some parts of Africa like South Africa. Therefore, favourable climatic conditions, amongst other factors, could be a potential factor that may have shielded the African continent from the proposed worse outcome in the face of the COVID-19 pandemic. Evaluating the sudden spike in cases (second wave) and/or even the partial or total lockdown in some countries during the beginning of spring supports the hypothesis of tropical weather hostility towards the effective transmission of SARS-CoV-2 in Africa and other tropical countries. However, an empirical study looking at temperature dynamics across countries with a broad temperature spectrum gradation does not support this claim (Jamil et al., 2020).

The second and third wave of COVID-19: will there be a continental resurgence in Africa?

A surge in SARS-CoV-2 infections has been observed in several European and Asian countries and North America, which raises increasing concern for Africa. With low reported COVID-19 fatality across Africa, a deadly surge on the continent could be devastating due to a more concerning weak healthcare system. Kenya has had lockdown in major cities in the past months; it is uncertain if Africa has witnessed the worst of the pandemic.

With the economic decline in most countries, there is a need to be more vigilant to prevent losing the gains that the African continent has made so far in curtailing the COVID-19
pandemic. While other continents grapple spasmodic wave of COVID-19, Africa could be witnessing an early sign of resurgence, as observed in few countries such as South Africa (Jassat et al., 2021), Nigeria (Duke, 2021), Kenya (Kiari et al., 2021), Algeria, Botswana, Ghana and Uganda. There have been speculations of herd immunity on the continent with the perception that subsequent outbreaks may be less severe, but this is yet to be validated via research.

The way forward
With the low reported COVID-19 cases in Africa, compared to Europe and the Americas, it is crucial to estimate the numbers of COVID-19 cases and related deaths by identifying persons on the continent who would voluntarily test for SARS-CoV-2 infection. The claims that certain herbal medicines could cure COVID-19 should be investigated and not automatically dismissed. Likewise, while researching treatment and vaccines, specific context strategies that fit each country should be considered and adopted to reduce COVID-19 severity, considering the differences in genetic makeup, climatic factors, use of orthodox medicines, prior exposure to multiple infections agents, among others. The one-cap fits it all concept may not apply in this case. While the necessary measures are essential and should be continued, measures with broader societal effects, such as restrictions on education and economic activities, should be continually reviewed and adjusted based on epidemiological data.

Increased testing of all suspected cases, contacts, and high-risk groups, including health workers, is necessary to detect sporadic cases and determine the actual number of cases on the continent to curb increased transmission. This strategy requires a well-established and coordinated healthcare system, with protective gears for health workers, adequate test kits, and decentralised testing centres with free or low-cost walk-in services.

We suggest a role for COVID-19 testing of dying patients in health facilities as postmortem testing will give a COVID-19 significant score, providing information on SARS-CoV-2-related deaths in many African countries (Giorgetti et al., 2021). In a Zambian postmortem surveillance study, SARS-CoV-2 was detected in 15.9% of the study cohort (Mwananyanda et al., 2021), further emphasising that COVID-19 cases in Africa are underreported due to inadequate testing. Reported COVID-19 case fatality rates (CFR) worldwide is more than 7%, with a lower percentage of 1% where whole populations like Switzerland have been tested and a higher percentage of more than 5% where only hospitalised patients were tested as in Italy (Mwananyanda et al., 2021). This necessitates more testing and seroprevalence studies to estimate the COVID-19 transmission rate and overall burden on the continent.

There is a need for community sensitisation to avoid stigmatisation of suspected cases and create psychological, mental, and emotional harm. Also, contextualising social mobilisation and community engagement, guided by evidence from surveys seeking to understand the local populations’ attitude and perception to COVID-19 preventive measures and survival, is necessary. The government and communities should provide a defined pathway of integration and social support. Such systematic approaches (integration pathway and strong community engagement) will likely ease stigmatisation around COVID-19 infection.

Providing situation reports and COVID-19 status updates should be mandatory for countries where government agencies can utilise multiple media outlets to inform and provide guidance to their citizens. Lessons from previous successful experience with epidemic controls in Africa reveal the need to implement medical and non-medical interventions, including behavioural changes. Individuals’ willingness to adhere and comply with government directives and measures such as wearing face masks in public places and others is critical to avoid a surge in the number of COVID-19 cases in Africa, as communities play essential roles in controlling epidemics. Also, standard prevention strategies should be regularly communicated to citizens as high SARS-CoV-2 transmission occurs at the early infection phase before symptoms develop.

It is pertinent for African governments to establish internal resource mobilisation and depend less on support and loans from major financial institutions and other countries. The COVID-19 pandemic has brought a global economic challenge, with several economies heading towards a recession. Thus, in-country funding from internally generated resources is needed to support different African countries in their COVID-19 strategic plans and implementation. The self-funding should be tailored toward short and long-term measures with a special Trust Fund to facilitate the implementation of COVID-19 related programs for increased awareness, sensitisation, surveillance, contact tracing/treatment, control and prevention. More competitive and feasible COVID-19 research funding that comprises multidisciplinary collaborations is needed for studies to unravel the extent and impact of community spread across Africa. Understanding infection and/or transmission progression will equip us with adequate knowledge to combat this pandemic.

Evidence of intensive research effort has been fruitful with the emergence of COVID-19 vaccines in less than one year since the pandemic. Hence, studies evaluating other potential factors like the lower prevalence of non-communicable diseases (Azarpazhooh et al., 2020) in Africa could unravel the reason for the less severe COVID-19 impact on the continent. These studies could be of utmost benefit in developing COVID-19 therapies, guiding public health interventions, and in case of future epidemics or pandemics. Also, constant evaluation of research agendas is imperative to tackle emerging issues, rather than earlier outdated predictions, as suitable responses will arise from understanding SARS-CoV-2 spread, characteristics and population dynamics.
Likewise, increased surveillance is important, with appropriate measures and interventions that are driven by quality research data. Information and scientific data sharing, including biological samples and genetic sequence data, are relevant to guide informed decision-making as research provides blueprints for policy formulation and implementation. Finally, data sharing on SARS-CoV-2 biology and spread from different countries has helped determine the effects of containment strategies and evaluate the emergence of mutations in the viral genome. This has increased scientific knowledge and will hopefully lead to evidence-based decision-making in controlling this pandemic. Although SARS-CoV-2 transmission may continue to spread in Africa, similar consequences experienced in Europe and the Americas could be avoided by continued vigilance and preventive actions implemented and supported by the “whole-of-society”, including researchers, healthcare professionals, government and the general public.

Data availability
No data associated with this article.

Author contributions
AJU conceptualised the study. AJU, MAO and ANH-A wrote the first draft of the manuscript, while SAO, AAN, LP, GAA and PKQ critically reviewed the manuscript for intellectual content. All authors reviewed the final draft of the manuscript and approved it for submission.

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