

VIEWPOINT: COVID-19

COVID-19 in Africa: Dampening the storm?

The dampened course of COVID-19 in Africa might reveal innovative solutions

By **Moustapha Mbow¹, Bertrand Lell^{2,3}, Simon P. Jochems⁴, Badara Cisse⁵, Souleymane Mboup⁶, Benjamin G. Dewals⁷, Assan Jaye⁸, Alioune Dieye¹, Maria Yazdanbakhsh⁴**

Coronavirus disease 2019 (COVID-19) has spread rapidly and extensively to most countries in the world, resulting in considerable mortality in Europe and the United States, as well as in numerous upper-middle-income countries in South America and Asia. Experts predicted millions of COVID-19 deaths in Africa because many countries in the continent rank poorly on the United Nations Development Programme's Human Development Index. However, more than 4 months after the first cases in Africa were detected, prevalence and mortality are still low. It remains unclear if Africa is really spared from substantial cases and deaths. However, differences between Africa and the most affected countries in reliable reporting and death registration, lockdown stringency, demography, sociocultural aspects, environmental exposures, genetics, and the immune system could help to explain the experience of COVID-19 in Africa.

Africa faces major health and socioeconomic challenges that should have allowed rapid transmission of COVID-19. These include a weak health system (per capita health expenditure of <\$50 in most West African countries compared with >\$2500 in Europe and the United States), population crowding, poverty, and unhygienic conditions (1). Population densities are very high in most African capital cities such as Dakar (12,617 persons/km²), Abidjan (11,155 persons/km²), or Lagos (13,909 persons/km²), whereas New York City has 7101 persons/km². However, although community transmission was reported in many major African cities months ago, the predicted number of cases and deaths has not yet been observed (see the figure). Low case numbers are often attributed to insufficient testing. However, many African countries implemented testing early on, and, based on the Our World in Data database (2), more tests per the number of cases were carried out than in other countries at similar phases of the epidemic (see

the figure). Regarding the number of deaths, few functional civil registration services and thus statistics exist on the continent, raising questions about the reliability of mortality data. Potential underreporting of COVID-19-associated deaths would not be specific to Africa, but the margin of error could be wider. To date, African countries have not indicated acute health emergencies; however, reliable age-stratified data are needed to fully grasp the COVID-19 situation in Africa to allow appropriate measures to be taken.

Measures such as travel restrictions, curfews, and school closures were implemented early in Africa compared with other continents, often before an African country had detected a case (fig. S1). These early responses might have resulted in fewer imported cases and reduced intracountry transmission, allowing sufficient time to prepare the constrained health systems for diagnosis and to prepare strategies for quarantine, contact tracing, and social distancing on a continent that already has experience in such practices to control epidemics such as Lassa fever and Ebola. Although it is likely that the early lockdown in Africa contributed to the slow spread, containment measures are not fully respected in many countries. Most people work in the informal business sector, such as in traditional markets, making strict lockdown measures impossible to implement. Recently, some African governments have been pressured to relax lockdown measures, for example, to carry out congregational prayers in mosques in Senegal. It remains unknown whether relaxation of containment measures will result in increased cases or if other factors are at play.

The majority of COVID-19-associated deaths occur in older people. Africa has a comparatively young population, with a median population age of 19.7 years for the continent versus 38.6 years for the United States. Africa's youthful population is reflected in the structure of age-stratified cases (fig. S2). Based on global age-specific case fatality rates for COVID-19 and the age demographics of Africa, COVID-19 deaths would be expected to be only four times (3), rather than the observed 40 times, lower than in

Europe or the United States. However, no aggregated data on age-specific case or death rates are available for the continent. There is substantial intergenerational mixing in Africa, and, with more cases of subclinical infections in the young, it could be a matter of time before expansive numbers of cases and deaths are recorded. Alternatively, a more rapid development of herd immunity among the youthful population might lead to fewer severe cases. Data from antibody tests (serosurveys) should clarify if transmission was more widespread with a high rate of asymptomatic and mild cases in African countries than in other countries.

The genetic characteristics of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and human genetics may be among the reasons for low incidence of severe COVID-19 in Africa. Although the relative contribution from Africa to the SARS-CoV-2 GISAID (Global Initiative on Sharing All Influenza Data) sequence database is small, the isolates found in Africa are representative of the different clades of SARS-CoV-2 found on other continents (fig. S3). Thus, it is unlikely that strains of SARS-CoV-2 in Africa have reduced virulence. Moreover, African-Americans constitute a disproportionate burden of deaths in the United States, so it seems unlikely that the lower mortality from COVID-19 in Africa is due to genetic factors. Nonetheless, the COVID Human Genetic Effort consortium aims to elucidate whether genetics can play a role in the patterns of disease worldwide.

SARS-CoV-2 infection leads to a heterogeneous outcome. About 80% of symptomatic cases are mild to moderate, whereas ~20% can develop severe respiratory disease and display high rates of mortality (4). The development of an effective adaptive immune response can limit viral infection, whereas uncontrolled activation of innate immune cells leads to a "cytokine storm" and hyperinflammation in the lungs, ultimately leading to acute respiratory distress syndrome (ARDS) and multiorgan failure (4, 5). Being able to suppress viral infection early or to temper excessive inflammatory responses are likely complementary mechanisms to prevent severe disease.

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Most convalescent symptomatic COVID-19 patients develop virus-specific neutralizing antibodies as well as specific CD4⁺ and CD8⁺ T cell responses (5). The efficiency and adequacy of these adaptive responses to clear viral infections depends on multiple factors, including past or concurrent infections with other pathogens. For example, antibodies directed to the four human coronaviruses that cause “common colds” could cross-react and neutralize SARS-CoV-2 in humans (6), and preexisting cross-reactive T cells can be found in individuals that have not been exposed to SARS-CoV-2 (7), suggesting previous exposure to related human coronaviruses could generate immunological cross-reactivity (7).

There are considerable differences in environmental exposures in Africa, compared with Europe or the United States. Noncommunicable diseases (NCDs)—such as cardiovascular diseases, obesity, and type 2 diabetes—are risk factors for severe COVID-19. These environmentally and behaviorally driven conditions are increasingly recognized in urban centers in Africa, and most COVID-19 deaths in Africa have been in older people with NCDs. However, infectious diseases such as HIV, tuberculosis, malaria, and other respiratory infections or those caused by helminths (parasitic worms) are prevalent in Africa, but there is currently little information on whether, or

how, these infections affect COVID-19 disease progression.

It is increasingly recognized that the immune system is shaped not only by genetics but also by environmental factors, such as exposure to microorganisms and parasites. This educates the immune system to protect against invading pathogens not only specifically but also nonspecifically through, for example, “trained immunity,” which involves the reprogramming of innate cells that, on secondary encounter with a pathogen, can show a stronger response (8) or “virtual memory” (9). Virtual memory T cells (T_{VM} cells) expand in response to cytokines such as helminth-induced interleukin-4 (IL-4), rather than through pathogen-specific antigens, leading to enhanced antiviral effector functions (9). Thus, it can be envisaged that T_{VM} cells are more prevalent in people in Africa owing to the higher exposure to such pathogens. This could contribute to the control of SARS-CoV-2. Additionally, as postulated by the “hygiene hypothesis,” early and chronic exposure to pathogens leading to relentless immune cell activation in harsh environments induces a strong regulatory immune response to counteract excessive inflammation (10).

The ability to prevent excessive inflammation could be a critical parameter that is associated with COVID-19 outcome. Recent data suggest that inflammatory alveolar

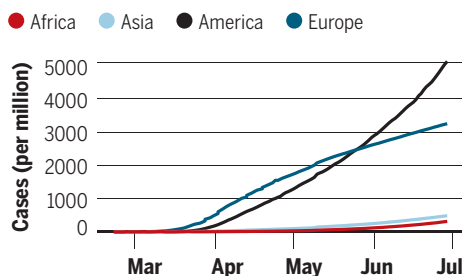
macrophages (AMs), which can arise from differentiation of recruited monocytes upon infection, are increased in the lungs of patients with severe COVID-19 (11). It is unclear whether these monocyte-derived AMs are an important source of the cytokine-release syndrome observed during SARS-CoV-2 infection or whether they are involved in the pathogenesis of ARDS. However, monocyte and macrophage inflammatory cytokines, such as IL-6, have been repeatedly observed to be a marker of severe COVID-19, and myeloid cells are thus likely to be associated with the hyperinflammation. Monocytes from African individuals with high exposure to pathogens can be less proinflammatory (12). Thus, their recruitment into the lungs might prevent high cytokine production and therefore lead to better outcomes of COVID-19. Moreover, the airway microbiota, as well as more distal gut microbiota, could play important roles in preventing or potentiating respiratory tract infections and modulating virus-induced inflammation, as has been shown for several respiratory viruses (13). The known variations in microbiota across geographical areas could thus also participate in modulating disease severity and should be studied.

Africa should be part of the roadmap for COVID-19 research. Although there are no available data on the immune responses in African COVID-19 patients, studies show

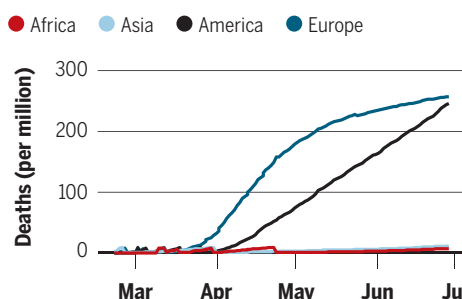
COVID-19 distribution and cases versus testing

The distribution of coronavirus disease 2019 (COVID-19) cases and deaths per 1 million inhabitants per continent reveals surprisingly low rates in Africa (left). This is despite comparable levels of testing per confirmed cases across continents (right). The dotted lines show the number of tests performed per number of detected cases. Data are from European Centre for Disease Prevention and Control COVID-19 situation updates, United Nations World Population Prospects 2019, and Our World in Data (2).

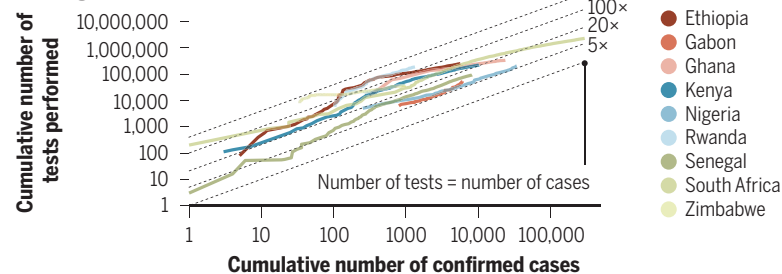
COVID-19 cases



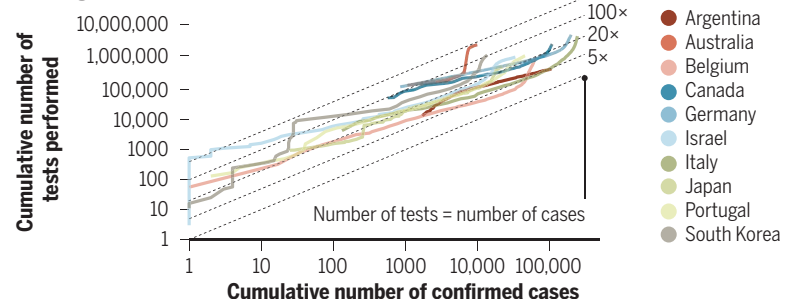
COVID-19 deaths



Testing in African countries



Testing around the world



clear differences in the activation, proinflammatory, and memory profiles of the immune cells not only in Africans versus Europeans but also among Africans with high and low exposure to microorganisms and parasites (14) (fig. S4). Does the difference in immunological profiles matter for the outcome of COVID-19 in Africa? This needs further investigation, and the pattern of COVID-19 in urban and rural Africa could be informative.

There are differences in opinion about whether the pattern of SARS-CoV-2 spread is different in Africa compared with that in the United States and Europe. So far, despite a paucity of data, it appears that the virus is spreading differently and potentially with an attenuated outcome in Africa. There has been limited testing of asymptomatic cases or of antibody titers. Therefore, it is unknown whether early interventions were successful in preventing transmission or whether there are differences in susceptibility between populations of different regions. Perhaps the COVID-19 pandemic can emphasize the need for widespread implementation of public health tools, such as high-quality data, accurate diagnostics for track and trace, good communication, and an effective vaccine. Early testing of vaccines in different regions of Africa is essential because the high degree of exposure to pathogens can limit some vaccine responses (15). The first COVID-19 vaccine testing is starting in South Africa (OxICov-19 Vaccine VIDA-Trial), and others are planned. Hopefully, this will stimulate the full participation of Africa in research into the critical factors that hold the key to innovative solutions in the fight against the pandemic. ■

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SUPPLEMENTARY MATERIALS

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CORONAVIRUS

Interferon responses in viral pneumonias

Are interferon-mediated antiviral immune responses beneficial or detrimental in COVID-19?

By Gary E. Grajales-Reyes and Marco Colonna

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak quickly developed into a pandemic in March 2020. To date, no vaccines or antiviral medications are available, and given the urgency, many clinical trials have started screening existing antiviral drugs for efficacy against SARS-CoV-2 infection. Among a variety of therapeutic approaches, the use of different types of interferon (IFN) as antiviral agents is under investigation owing to promising outcomes in other coronavirus-induced pathologies (1). Through different mechanisms and effector proteins, IFNs play an important role in the inhibition of viral replication (2). On pages 712 and 706 of this issue, Major *et al.* (3) and Broggi *et al.* (4), respectively, describe the mechanisms by which IFN- λ responses contribute to pathogenesis in viral pneumonias. Conversely, on page ZZZ, Hadjadj *et al.* (5) studied peripheral blood responses from a cohort of 50 patients with coronavirus disease 2019 (COVID-19), demonstrating that critically ill patients have reduced IFN responses paired with a proinflammatory response.

IFNs are important cytokines of the innate and adaptive immune system and are classified into three main types: I (α or β), II (γ), and III (λ). During viral infections, pattern-recognition receptors detect viral nucleic acids, inducing the production of IFNs. The expression of type I, II, and III IFNs is not redundant among all the IFN-producing cells. In particular, expression of IFN- λ is tissue specific and is mainly produced by dendritic cells, epithelial cells, and hepatocytes. In humans, IFN- λ includes four members (IFNL1 to -4), all of which bind and induce signaling through the heterodimeric IFN- λ receptor (IFNLR) (6), which is mostly restricted to epithelial cells, dendritic cells, and neutrophils (7, 8). Signaling through the IFNLR triggers an intracellular signaling pathway, which in turn induces expression of a group of IFN-

stimulated genes (ISGs) (9). IFNLR signaling also induces expression of the tumor suppressor p53, which limits viral replication by enhancing IFN signaling and causing cell cycle arrest of infected cells (10, 11).

Although IFN- λ has antiviral effects, it has been shown that in mice, IFN- λ produced in response to influenza virus infection increased susceptibility to pneumonia caused by subsequent infection with methicillin-resistant *Staphylococcus aureus* (called superinfection) (12). IFN- λ caused expansion and restructuring of the nasal microbiota, as well as impaired epithelial barrier function, which allow bacteria to invade and colonize the tissue. Consistent with this observation, Broggi *et al.* showed that amounts of IFN- λ messenger RNA (mRNA) from bronchoalveolar lavage fluid and naso-oropharyngeal samples correlated with disease morbidity in SARS-CoV-2-positive patients. They found that the association between morbidity and IFN- λ observed in humans was reproduced in mice treated with intratracheal polyinosinic:polycytidylic acid [poly(I:C)], a synthetic double-stranded RNA that mimics viral RNA and induces innate immune responses. Intratracheal poly(I:C) administration was also associated with impaired lung epithelial barrier function.

SARS-CoV and influenza virus infect lung alveolar epithelial cells. As viral replication proceeds, lung epithelial cells die because of cytopathic effects as well as immune-mediated damage. Recovery is then achieved through epithelial cell proliferation and differentiation. Both Major *et al.* and Broggi *et al.* show that after influenza virus infection or intratracheal poly(I:C) challenge, respectively, IFN- λ impairs lung epithelial cell proliferation during recovery. Major *et al.* further found that IFN- λ impairs differentiation of alveolar epithelial progenitor cells into secretory and multiciliated cell subtypes. In accordance, both groups identified that the impaired epithelial proliferation is dependent on expression of IFNLR. Mice in which the *Ifnlr1* gene is deleted (*Ifnlr1*^{-/-}) had improved epithelial proliferation after an influenza virus or poly(I:C) challenge. This phenotype was mediated by lung stromal cells because

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Supplementary Materials for **COVID-19 in Africa: Dampening the storm?**

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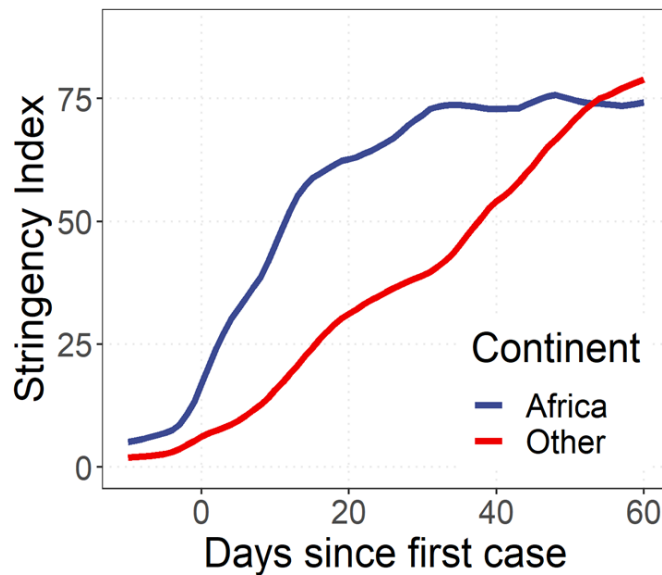
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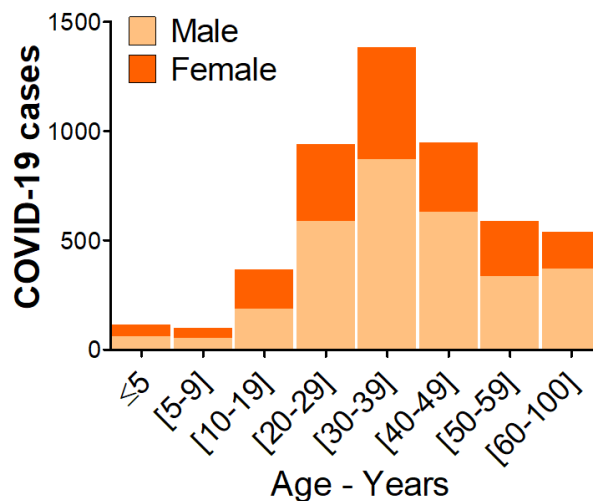
This PDF file includes:

Figs. S1 to S4
List of Data Sources

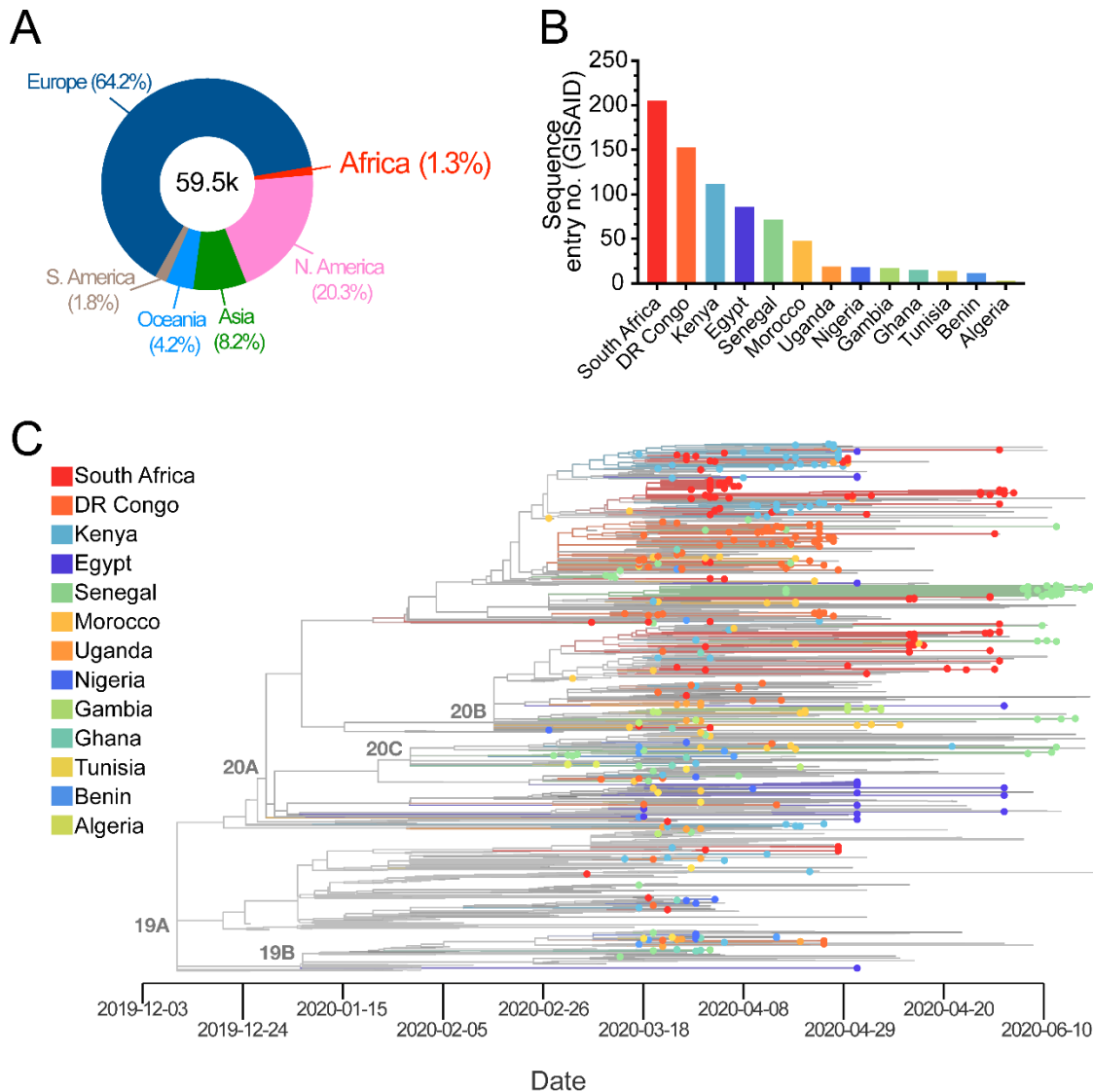
Supplementary material



Supplementary figure S1: Stronger government stringency response in Africa. Stringency response implemented days after the first case was reported. Comparison of indicators such as travel restrictions and school closures (stringency index), between 47 African countries for which data are available and the 47 non-African countries that currently have the most cases [Source of data: Oxford covid-19 government response tracker (1)].

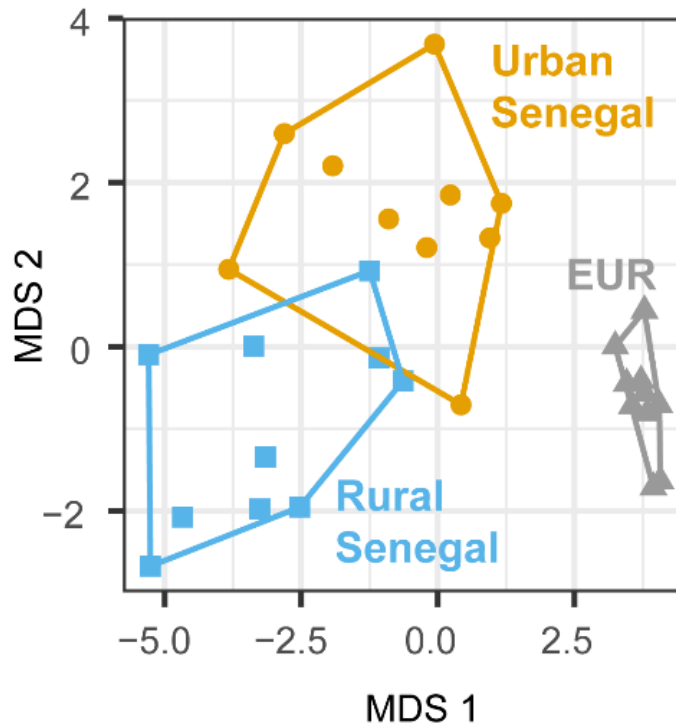


Supplementary figure S2: Age distribution of COVID-19 cases in Africa reflecting the younger age of the population on the continent. Age- and sex-stratified COVID-19 cases in Africa [Source of data: COVID-19 WHO African region (2)].



Supplementary figure S3: Genetic variation of SARS-CoV-2.

Distribution in percent of SARS-CoV-2 sequences in GISAID database per continent **(A)**. Distribution in total numbers of SARS-CoV-2 sequences originating from African countries in GISAID database **(B)**. Phylogenetic tree showing divergence of SARS-CoV-2 genome sequences since 8th of December 2019, indicating that isolates found in Africa are representative of the different clades of SARS-CoV-2 on other continents **(C)**. [Source of data: Global Initiative on Sharing Avian Influenza Data (GISAID) initiative (3) and Nextstrain Real-time tracking of pathogen evolution (4)].



Supplementary figure S4: The variation in the immune response along an urban to rural gradient. Multi-Dimensional Scaling (MDS) illustrating z-scaled levels of activation, maturation and cytokine production markers in CD4+ T cells, B cells and monocytes from individuals from Europe (EUR), Urban Senegal and Rural Senegal. MDS was performed using the cmdscale function in R [Source of data: reference 14 of the manuscript]

List of data sources used for supplementary figures

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