Review

Addressing Inequality in the COVID-19 Pandemic in Africa: A Snapshot from Clinical Symptoms to Vaccine Distribution

Ana Catarina Pêgo, Illyane Sofia Lima and Raffaella Gozzelino *

NOVA Medical School Research, NOVA University of Lisbon, 1150-082 Lisbon, Portugal
*   Correspondence: raffaella.gozzelino@nms.unl.pt or raffaellagozzelino@gmail.com

Abstract: On 30 January 2020, WHO declared COVID-19 a public health emergency of global concern. COVID-19 became pandemic on 11 March 2020, and spread unprecedently. No country was prepared to face its impact. Major fears started to be expressed for Africa, where dramatic consequences were expected, due to the weakness of health systems. In this review, we related major concerns, at that time but still present, regarding the limited resources in terms of qualified physicians and researchers, as well as the scarce funds to purchase essential medical equipment and improve hospital infrastructures. The difficulties to provide proper care became an undeniable mark of inequality, highlighting the need to empower local capacity and raise preparedness against infection outbreaks. The transmissibility of genetic variants affecting African nations, the immunopathology underlying comorbidities, sequelae, and pre-existing conditions, often related to changes in iron metabolism and enhancing COVID-19 severity, were described. The obstacles in adopting standardized prevention measures were highlighted, along with testing capacity biases and inequity of healthcare access and vaccine distribution. By providing a better understanding of the COVID-19 pandemic in Africa, we draw attention to the need for collaborative efforts to leverage the quality of healthcare and research in this continent.

Keywords: SARS-CoV-2; COVID-19; infections; immunopathology; iron; vaccination inequity; Africa

1. COVID-19 in Africa

Africa is the second most populated continent, with around 1.3 billion people (17% of the world population) [1]. It comprises 54 independent nations, many of which are referred to as fragile states [2,3]. Original predictions indicated that Africa would be disproportionately affected by COVID-19 [4], also in view of the difficulty of implementing effective measures of social distancing [5]. The first case of COVID-19 was reported in Egypt on 14 February 2020 [6]. Then, imported cases started to be detected in other African nations, as most Europeans were trying to escape the dramatic reality they were experiencing [7]. African governments were highly sensitized to seeing countries with large economies being defeated by the virus and started to close borders and isolate nations from foreign entry [7]. Although in Africa local transmission increased slowly [7], the limited financial and qualified human resources to overcome the deadly disease forced this continent to preventively lock down [5,8]. The youthfulness of the African population is the most plausible explanation for reduced severity of COVID-19 in this continent. The average age is 19.7 years, and 60% of the population is younger than 25. As we know, severe symptoms predominantly affected the elderly population [9], who suffered from sub-chronic impairments of the immune system. In Africa, immunity is linked to multiple pathogen exposures [10], which shape the immune response. This continuous activation is capable of reprogramming immune cells [11] and providing them with the ability to respond differently to microbes [12]. This is an advantage which allows individuals to better cope with infection, including during childhood. In the context of COVID-19, this notion was demonstrated by comparing the immunity elicited upon infection in Belgian, Canadian, Ecuadorian, and South African cohorts, the latter showing a reduced functional response of immune cells. Lifestyle trends, scarce consumption of processed food,

climate, and environmental aspects are other factors that might have contributed to mitigating the dramatic effects caused by the pandemic [13]. This notion was supported by evidence showing that environmental parameters were able to contradict initial predictions and reduce virus lifespan [14,15]. While the low temperatures and humidity of the northern globe hemisphere facilitated the virus' survival [16], the warm African climate was shown to reduce the risk of COVID-19 infection [17]. The effect of sunshine UV rays acted synergistically, on one hand compromising viral stability and diminishing disease transmission, and on the other causing a beneficial effect on the host. Individuals presenting an increased level of vitamin D were able to elicit a more efficient activation of an immune response against the virus [18]. It is also worth mentioning that the windy weather in some countries was also considered an advantage. It negatively affected viral spreading [19] and contributed to dispersing viral pathogens, lowering disease transmission. Hence, the growth curve for COVID-19 in Africa was inversely correlated to average temperature and wind speed [20].

However, a shift from this initial positive scenario occurred when multiple SARS-CoV-2 variants started to appear. By the end of 2020, most African countries underwent a second wave of infection, with a 30% growth in weekly incidence and daily average of new cases, in relation to the peak of the first COVID-19 wave [21]. Controversial suggestions were publicly advanced, with people proposing on international television channels to let the continent reaching heard immunity, a possibility that was finally not considered. Whether this was due to a global voice raised against those statements or to the fear of a potential "boomerang effect" is still not clear. Indeed, the many efforts made to contain the COVID-19 pandemic could have been jeopardized with a reestablished mobility between continents. The concern that implemented measures might have been of no use is possibly the reason for which "common sense" prevailed.

In March 2023, nearly 180,000 fatalities were reported in Africa vs. almost 8 million deaths registered worldwide. According to the WHO, South Africa and Morocco were the most affected [3,22]. In this regard, it should be highlighted that over 50% of African citizens reside in rural areas, with limited interaction with travelers or urban communities that could potentially carry the virus [23]. When compared to other continents, the rate of foreign travel to Africa is relatively low. South Africa and Morocco have the highest rates, ranking, respectively, 22nd and 28th worldwide. This may explain why these countries showed the highest number of cumulative COVID-19 cases in Africa [24].

Concerns regarding a possible discrepancy between predicted and confirmed cases stood out. The reduced morbidity and mortality registered in the African continent was inconsistent with the results obtained from seroprevalence tests [25]. Antibodies were detected in 10–30% of the African population. However, this percentage also raised numerous discussions, as positivity relied on the testing capacity of the country where the assay was performed [8]. No nations had the financial resources to purchase tests for all suspected cases. So, while there were countries who received more assistance than others from state cooperation and international donations, the percentage of conducted tests was not comparable to the developed world. While South Africa conducted a total of 54,224 tests per million people, Egypt and Nigeria carried out 1317 and 1504 tests, respectively. In the UK, the number of conducted tests was 266,500 per million people, and in the US it was 195,072 during the same period [26].

However, despite the overall lower number of individuals that were reported to have developed severe symptoms [4], COVID-19 in Africa is still a threat. The precarious situation, characterized by a variety of infectious diseases, malnutrition, and limited access to healthcare, has worsened since the pandemic occurred [27,28]. In addition, the inequality of vaccine distribution as well as of population adhesion to vaccination programs hindered African response to COVID-19 [29].

2. SARS-CoV-2

It is known that thousands of viruses circulate silently in wild mammals and can infect humans by zoonotic spillover. Among zoonotic diseases, coronaviruses have already caused previous unexpected outbreaks in the past [30–32]. Coronaviruses are enveloped,

non-segmented, positive-sense, and single-stranded RNA viruses [33], with the largest genome [34,35]. Their size varies from 26,000 to 33,000 bases. Coronaviruses are divided into four genera: Alphacoronavirus (α-CoV), Betacoronavirus (β-CoV), Gammacoronavirus (γ-CoV), and Deltacoronavirus (δ-CoV). The subtype β-CoV has been responsible for three outbreaks in the last two decades. These are the Severe Acute Respiratory Syndrome (SARS), the Middle East Respiratory Syndrome (MERS), and the COVID-19 pandemic [35], which was first reported by Chinese health facilities in December 2019 [36].

Receptor recognition is a fundamental determinant of virus infection in humans, and ACE2 was referred to as the entry door for SARS-CoV-2 [37–39]. Upon the binding of SARS-CoV-2 to ACE2, the S1 subunit of the spike protein undergoes a conformational change, exposing the S2′ cleavage site in the S2 subunit [40]. This is cleaved by different proteases, among which is the transmembrane protease serine 2 (TMPRSS2) [41], located at the cell surface [42,43]. The creation of a fusion pore allows the viral genome to subsequently reach the host cell cytoplasm [43], where it begins to translate the viral genome [44]. Virion-containing vesicles are formed, and they fuse with cell membranes to release new viruses [45–47].

3. Genetic Variants of SARS-CoV-2 Reported in Africa

Virus variants emerged since the outbreak and mostly affected the spike protein, which became the target of vaccine and monoclonal antibody production (Figure 1) [48,49]. The first variant was known as D614G. It appeared in April 2020, replacing the original SARS-CoV-2 by June 2020 [48,50]. A few months later, another variant was reported in the UK and was named Alpha (B.1.1.7) [50]. Many additional mutations occurred since then, showing distinct effects, in terms of infection spread and symptom severity, related to the affected region. In the spike protein, mutations like N501Y increased virus transmissibility [48]. Similar effects were also identified in variants affecting the non-spike and nucleocapsid regions, resulting in different sub-lineages [50]. South Africa was the incubator of the Beta variant (B.1.351) [50], a highly transmissible strain, sharing D614G and N501Y mutations with the Alpha variant. Unexpectedly, B.1.351 was less effectively neutralized by conventional therapies [48]. While the country was severely affected, Brazil reported a new variant, the Gamma (P.1) variant [51], causing an infection rate of approximately 75%. Mutations in the spike protein region [48,50] and in the amino-terminal domain [50] characterized P.1. This variant was not reported in Africa, raising concerns regarding how much sequencing the continent could afford. Nevertheless, the Delta variant (B.1.617.2) started to spread. From India, it reached Africa, where it significantly increased the morbidity and mortality rate of many fragile nations [3,52]. The same occurred with the Kappa (B.1.617.1) variant, although its transmissibility and number of sub-lineages were lower [50]. Despite all these mutations, the variant that prevailed in Africa was Omicron (B.1.1.529) [3,52–54]. The many genetic changes affecting Omicron [55] increased its infectivity [56], but reduced the risk of the virus causing severe clinical outcomes. Hence, this variant became less lethal [57]. Since then, different mutations were identified in Omicron and many sub-variants were reported [58–60]. Some emerged as lineage combinations, and their evolution is still closely followed.
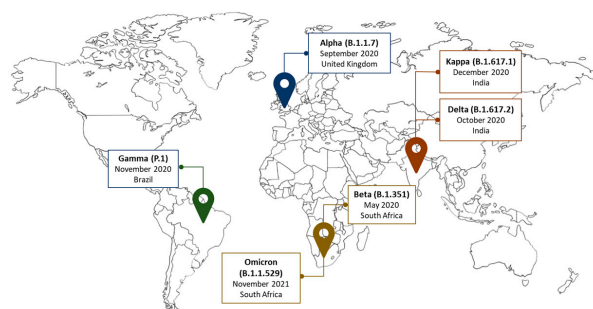

Figure 1. Variants of concern. RNA viruses, such as SARS-CoV-2, constantly evolve. Some mutations can provide the virus with a selective advantage, like increased transmissibility.

4. The Transmissibility of SARS-CoV-2 and the Difficulty of Applying Standardized Protection Measures in Africa

The fear of unprecedented mortality in Africa due to the COVID-19 pandemic grew exponentially when it was realized that the best healthcare provided in the developed world was not sufficient to stop the lethality of SARS-CoV-2. The virus was shown to replicate from 5 to 11 days [61,62]. Then, common symptoms, like fever, fatigue, and dry cough, began to appear [63]. Malaise and myalgias were also reported [64], as well as headache, abdominal pain, diarrhea, nausea, and vomiting [65]. While anosmia and ageusia were considered early markers of COVID-19 [64], shortness of breath was suggestive of a worsening disease stage [65]. Hence, protection measures to mitigate the infection started to be standardized. However, soon after their implementation, it became clear that they were designed for different realities than that in Africa. The virus was transmitted through close contact with infected individuals and the inhalation of viral-containing particles in the form of microscopic aerosols [66–73]. Thus, how could distance be maintained among people that mostly live of the informal sector or running small restoration businesses? How could home confinement be followed by people belonging to economically devasted communities, in which street selling remains the only source of sustenance? The difficulty of adopting standardized norms also referred to preventive measures of hygiene. Besides alcohol shortages, inequalities were highlighted even upon recommendations of simple actions, such as hand washing. In Africa, only one third of the population has regular access to clean water [74]. So, not stressing measures that required financial support to be implemented, many took for granted the privileges of living in developed countries. When scientific evidence found active viruses in biological samples, like urine [75,76] and feces [75,77–79], even after patient recovery [77,80], many concerns were raised in the continent, as most African citizens do not have access to private and clean sanitary facilities. Hence, viral infectivity was also expected to significantly grow because of open drains and squat toilets, lacking flushing water systems [81]. Accordingly, an enhanced number of cases started to be reported in countries where open defecation was a common practice. The lack of proper infrastructures for human waste management was seen as an additional risk for viral spreading [82]. This emphasized that despite the effort made to educate society on how to avoid infection, the applicability of many measures caused a double-edge feeling. The rules globally adopted contradicted many socioeconomic and cultural aspects associated with an increased risk of viral transmission, such as breastfeeding, which was referred as one of the routes for SARS-CoV-2 transmission [83]. In Africa, approximately 40% of infants are exclusively breastfed [84,85], a percentage below the WHO's Global Nutrition Target of a 50% prevalence to be reached in 2025 [86]. The hypothesis that those women could have turned into disease incubators stood out. Concerns were also expressed in the case of intrauterine spreading [87], as the impact of COVID-19 became more evident in reproductive healthcare. In over 115 evaluated countries, including almost 50 African nations, maternal and child mortality rates increased monthly by 38.4% and 44%, respectively [88]. Nowadays, since COVID-19 does not pose a deadly threat to the world anymore, efforts should be made to evaluate Africa's response to viral infectivity, teaching lessons for future outbreaks and promoting policies to leverage healthcare.

5. The Sequelae Caused by SARS-CoV-2

Systemic and neurological symptoms have been detected in COVID-19 patients, even 12 months after hospital discharge. The reason is that ACE2 is expressed in different organs, like lung alveolar epithelia, small intestine, renal proximal tubules, gallbladder epithelium, cardiomyocytes, testicular Sertoli cells, Leydig cells, and the brain [46]. The binding of SARS-CoV-2 to ACE2 might affect all those organs [46,89]. This topic was addressed in a comprehensive systematic review and meta-analysis, evaluating pulmonary complications long after the infection. Almost 50% of survivors showed multiple sequelae [90,91], among which were dyspnea, oxygen dependence, and fibrotic lung disease [92]. Radiographic abnormalities persisted in 81% of patients that suffered from severe pneumonia [93]. Fa-

tigue was reported by approximately 30% of recovered individuals and often turned into cardiovascular impairments. In 14.8% of COVID-19 survivors, abnormal palpitation and thrombosis [90], as well as myocarditis and myocardial infarction [92], were reported. About 12% of patients revealed psychiatric and neurological symptoms [90], which included cognitive and behavioral deficits, along with depression, anxiety, insomnia, and taste dysfunction [92].

While this characterization was performed in developed countries, we still do not know if it also applies to African nations. Further studies should be conducted to provide a picture of the long-term sequelae caused by COVID-19 in this continent [94]. Investigations carried out in South Africa and sub-Saharan Africa showed that 47% of hospitalized patients and 19% of non-hospitalized patients experienced persistent symptoms after six months [91]. Long-term sequelae were poorly detected in patients infected with the Omicron variant [95]. When occurring, long-lasting effects were mostly complained of by the elderly and female population [92]. However, it is worth mentioning the difficulties in detecting COVID-19 sequelae in Africa, due to underlying health conditions, like other infection, malnutrition, and poor access to quality care.

6. The Comorbidities Underlying COVID-19 Severity in Africa

Among the comorbidities enhancing the severity of COVID-19, non-communicable diseases were recognized worldwide as a prevalent risk factor for poor clinical outcomes. Their incidence in Africa is a major concern [52,96]. Non-communicable diseases are expected to be the primary cause of mortality in African nations by 2030 [97]. The Democratic Republic of the Congo, Nigeria, Ethiopia, and South Africa present the highest rates, considered as a potential explanation for the increased number of reported severe COVID-19 cases. According to the Global Burden of Disease studies, the incidence of non-communicable diseases in Africa has also been linked to the growing adoption of the Western lifestyle [98–100].

Among those pathologies, diabetes mellitus stood out [101]. In Africa, the number of diabetic individuals is 24 million and is projected to increase by 129% in 2045, reaching 55 million people [102]. Diabetic patients were more likely to manifest severe COVID-19 symptoms. Their compromised immune system, hypercoagulable pro-thrombotic state, endothelial dysfunction, and vascular inflammation [103] led to diabetes mellitus being a major contributor to COVID-19-induced complications and mortality [104–107]. According to WHO, during pandemic times, the fatality rate of diabetic patients was 10.2%, as assessed in 13 sub-Saharan countries. Conversely, in non-pandemic times, it was 2.5% [108].

Another risk factor for the appearance of severe COVID-19 symptoms was cardiovascular diseases [109]. Their prevalence varies from 0.1% in Sudan, where coronary events prevail, to 20% in Mozambique, where individuals mainly develop endomyocardial fibrosis [97]. Childhood rheumatic heart disease is also widespread in sub-Saharan Africa [110], ranging from 0.2% to 3% [111–115]. In terms of long-term sequelae, the occurrence of thrombosis and cardiorenal syndrome, upon COVID-19 infection, prevailed [94]. However, cardiovascular pathologies are also triggered by other highly prevalent infections, among which are HIV and tuberculosis [116], alerting of the difficulty in discriminating cardiovascular impairments caused by SARS-CoV-2 or other pathogens. In Africa, almost 50% of the individuals that suffer from tuberculosis show symptoms of pericarditis [97]. Its severity was significantly worsened by COVID-19 when individuals also carried HIV [117]. Similar results were even obtained in relation to the number of casualties [118]. Inflammation, elicited by SARS-CoV-2, exacerbated heart and blood vessel damage, as evidenced by the tropism of the virus for these cells [119,120]. Also, fibrosis-altered lung function and chronic obstructive pulmonary disease were reported as long-term COVID-19-induced sequelae in patients with tuberculosis [94,121,122]. Coinfections are prevalent in Africa. In the presence of different pathogens, the response to COVID-19 was impaired [52], as revealed in a study including 17,871 participants infected with SARS-CoV-2 [123].

Another concern drawing attention to severe COVID-19 symptomatology was obesity. According to WHO, 20% of adults and 10% of children and teenagers in South Africa, Nige-

ria, Mozambique, Uganda, Tanzania, Zambia, Zimbabwe, Kenya, Malawi, and Ethiopia, were expected to be classified as obese by December 2023 [124]. Although a causal relationship between obesity and COVID-19 was not fully established, evidence suggested they are strictly related. Hospitalized COVID-19 patients manifesting adult respiratory distress syndrome were often obese [125–128] and presented associated comorbidities [129]. However, differences in obesity epidemiology might have impacted the severity of COVID-19, especially when referring to urban regions. Most African people living in rural areas suffer from malnutrition, which is known to impair immune response and increase symptom severity [130]. In Angola, Liberia, Tanzania, Burkina Faso, Chad, Mali, Niger, Sudan, as well as in the Northern African region and Yemen, malnutrition and iron deficiency prevail, presumably justifying the high mortality caused by COVID-19 [131].

The prevalence of diseases related to disruption of iron metabolism also highlighted the possibility that deficiency of this metal might have played an important role in the fight against COVID-19 in Africa. Iron is a vital element, ensuring the development and survival of many organisms [132]. Viruses also need iron to proliferate, as it is required for the synthesis of their genetic material and energy production. Despite the lack of studies evaluating the correlation between iron levels and COVID-19 severity in Africa, numerous investigations were conducted in developed countries. In human volunteers, the exposure to norovirus was associated with the induction of hypoferremia, caused by an increased hepcidin, the hormone regulating iron absorption and circulating levels [133]. Dysregulation of iron homeostasis in COVID-19 patients was observed since the beginning of the outbreak [134]. The analyses of 99 patients, hospitalized in Wuhan Jinyintan Hospital with COVID-19-induced pneumonia, showed tissue iron overload and increased serum ferritin, the neutralizing protein storing iron within its subunits [135]. A higher production of pro-inflammatory cytokines directly linked to iron levels, like IL-1, IL-6, INF-γ, and TNF, was associated with a poor prognosis [136,137]. The cross-talk between inflammation and iron metabolism led researchers to investigate if hepcidin levels could predict the fatal outcome of COVID-19 infection [138]. Patients with hepcidin levels below 394 ng/mL were found to be more likely to survive. Higher levels of hepcidin were shown to increase inflammatory markers, like CRP and ferritin, as assessed in a descriptive study conducted with 5700 COVID-19 patients [127]. Hypoferremia was manifested in almost all ICU-admitted COVID-19 patients [139] and was associated with expression of organ damage markers, like aspartate aminotransferase-AST and lactic acid dehydrogenase-LDH [140,141]. Severe COVID-19 was also linked to low levels of hemoglobin, possibly as a consequence of the lower iron levels available for its synthesis. This negatively impacted erythrocyte production, as confirmed by the decrease in erythropoietin [142]. Its release also depends on the ability to sense hypoxia [141,143], and patients suffering from severe hypoxemia were found with lower levels of serum iron [144]. The decrease in hemoglobin functioning might also be explained by the ability of SARS-CoV-2 to use CD147 and CD26 receptors on erythroid cells as an alternative entry into cells [145,146]. CD147 is also known as basigin or EMMPRIN and was shown to directly bind to the spike protein [145]. However, no evidence of basigin variants was found in a genomic study evaluating 131 COVID-19 patients [147], and no role was detected for this receptor in viral infection assays in lung cells [148]. It has been postulated that SARS-CoV-2 can also interact with hemoglobin through CD26 [134], binding the S1 domain of the spike protein [149]. Its role in regulating hematopoiesis, influencing the production of colony-stimulating factors [150], raised the hypothesis that erythropoietic-based adjuvants could be used as potential therapeutic options. Given that the activation of immune cells relies on iron [143], low levels of this metal justified the impaired T cell response reported in COVID-19 patients [144,151].

7. The Immune Response to SARS-CoV-2 in Africa

In Africa, the immune system is confronted with unique challenges, including a lack of specific micronutrients or essential elements promoting adequate responses. The impaired development of T and B cells [152] influences the ability to cope with SARS-CoV-2

infection [153], and patients developing severe symptoms presented malnutrition as a common denominator. A study conducted in Nigeria with 4311 COVID-19 patients showed that 12.9% were malnourished. The risk of death in this group increased by 76% and the risk for long hospitalization by 105% [154]. Immune function is also affected by mineral deficiencies [155], among which iron deficiency stood out. With malnutrition, it was likely to be one of the main factors responsible for the increased mortality rate in sub-Saharan Africa. The countries mainly affected by malnutrition and iron deficiency were those reporting an enhanced lethality, such as Angola, Liberia, and Tanzania; Burkina Faso, Chad, Mali, Niger, and Sudan in the Sahel strip; and the Middle East and the Northern African region [131]. Knowing that iron is essential for the expansion and differentiation of effector and memory immune cells, many concerns were raised regarding the potential efficiency of vaccination programs [138,156]. Studies on hypoferremia indicated this condition as capable of inhibiting the response to vaccines [157]. This notion was also confirmed in Southern coastal Kenya in an investigation of mandatory vaccination programs in a birth cohort [158].

Pre-existing cross-reactive immunological responses to common cold coronaviruses and other infections are believed to have reduced COVID-19 severity in Africa. Hospitalized patients, with high levels of IgG antibodies against common cold coronaviruses, were shown to develop mild COVID-19 [159]. Blood samples collected in pre-pandemic African cohorts found those individuals to be ten times more serologically reactive to SARS-CoV-2 [160]. Cross-reactive immunity against SARS-CoV-2 nucleocapsid protein was detected prior to the COVID-19 pandemic in a study conducted in Uganda [161,162]. Exposure to multiple infections is thought to have protected patients from severe COVID-19, as in countries with a higher prevalence of malaria reporting a lower number of COVID-19 cases. This negative correlation was found in 53 African countries [163] and linked to the higher expression of an epigenetic modification to histone H3, H3K4me3. The result is the induction of a trained immunity [164], which persisted after recovery and was shown to be capable of generating a strong response against secondary stimuli, like SARS-CoV-2 infection [165].

Sickle cell disease (SCD) is another prevalent pathology in Africa. It increased the risk of respiratory infections and pulmonary complications in response to COVID-19 [166].

HIV is also a comorbidity capable of influencing the outcome of SARS-CoV-2 infection. Natural and vaccine-induced immune responses against SARS-CoV-2 were less effective in HIV carriers, particularly when not under antiretroviral therapy. No significant differences were found in a study conducted in Western Kenya, including 582 participants [167], regarding the prevalence of SARS-CoV-2 antibodies in patients with and without HIV (3.1% vs. 4%, respectively). However, only 3.3% of this cohort developed SARS-CoV-2 antibodies [168]. Investigations carried out in other studies, including 104 individuals, revealed that COVID-19 in HIV patients did not increase the risk of death [169].

Co-infections with tuberculosis were another major concern. In a South African cohort of more than 3 million tuberculosis patients, co-infections with COVID-19 were shown to increase the risk of death and to prolong the recovery time by 2.17 folds [169–172]. Individuals with latent tuberculosis presented a higher lymphocyte count, when developing COVID-19 [165,173], which lead to an early activation of adaptive immunity and antibody production [173]. Co-infections were characterized by elevated IL-6, which was linked to poor outcomes [174]. Higher levels of neutralizing antibodies against SARS-CoV-2 (IgM, IgG, and IgA) were found in asymptomatic COVID-19 patients with latent tuberculosis, presumably due to previous exposure to *M. tuberculosis* antigens that activated memory T cells [175]. Co-infection with active tuberculosis decreased lymphocyte count and cytokines production [176,177]. Triple infections, i.e., patients diagnosed with HIV, tuberculosis, and SARS-CoV-2, show a significantly reduced lymphocyte count and antibody response against COVID-19, associated with higher levels of inflammatory markers, including D-dimer and ferritin [65,178–181]. Although, so far, no differences in post-COVID-19 manifestations were found in vaccinated and non-vaccinated individuals, no distinctions were made

between individuals exposed to partial or complete vaccination programs, as revealed in a South African study [182–186].

Hence, understanding co-infection behavior in Africa might provide new insights about the efficacy of vaccination programs against SARS-CoV-2 [169].

8. Vaccine Development

According to the WHO, as of December 2020, there were over 200 vaccine candidates, and at least 52 were already approved [187]. Most targeted the spike protein of SARS-CoV-2 [188,189]. Among the platforms used for vaccine development, the mRNA-based technology was the most effective and a deserved Nobel Prize was attributed to Prof. Dr. Katalin Karikó and Prof. Dr. Drew Weissman for their discoveries enabling their production [190].

Table 1 illustrates the characteristics of the vaccines that were commonly used: mRNA-1273 and BNT161b2, from Moderna/NIAID and Pfizer/BioNTech, respectively. Presenting similar mechanisms and efficacies over 90% [191,192], the development of mRNA vaccines was based on the injection of a lipid-nanoparticle-encapsulated synthetic nucleotide sequence that codes for the viral spike protein [192–195]. This induces a coordinated immune response, in which the mRNA is presented to antigen-presenting cells and is subsequently recognized by T lymphocytes [193,195].

Table 1. Summary of COVID-19 mRNA vaccines that were used globally.

Vaccine Type	Name	Characterization	Company	Vaccine Efficacy	Storage	Systemic Reactogenicity	References
mRNA vaccines	BNT162b2	Nucleoside modified mRNA encoding full length S protein (stabilized in prefusion conformation)	Pfizer, BioNTech, Fosun Pharma	95% effective in preventing symptomatic COVID-19; 100% effective in preventing severe COVID-19	Six months at −70 °C or stored at RT for less than 2 h when undiluted.	Fatigue, headache, fever, and chills. Swelling, pain, and redness at the site of injection.	[191,196]
	mRNA-1273	Synthetic mRNA encoding the pre-fusion stabilized S protein	Moderna	94.1% effective in preventing symptomatic COVID-19 100% effective in preventing severe COVID-19	Stored for less than 12 h at RT; for 30 days at 2 to 8 °C; more than 1 month stored at −25 °C to −15 °C.	Swelling, pain, and redness at the site of injection. Fatigue, headache, fever, vomiting, chills, myalgia, urticarial, and arthralgia.	[192,196]

However, viral vector vaccines, using replication-deficient viruses, also showed promising results. These genetically engineered non-replicating adenovirus vectors, containing a DNA sequence expressing the full length of the spike protein of SARS-CoV-2, present characteristics shown in Table 2. Once endocytosed by host cells, the virus is translocated to the cell nucleus, where it releases the DNA necessary for the transcription of the spike protein [197].

Table 2. Summary of COVID-19 viral vector vaccines that were used globally.

Vaccine Type	Name	Characterization	Company	Vaccine Efficacy	Storage	Systemic Reactogenicity	References
Viral Vector Vaccines	ChAdOx1 nCoV-19 (AZD1222)	Replication-deficient chimpanzee viral vector with SARS-CoV-2 S protein	University of Oxford, AstraZeneca	64.1% after 1st dose and 70.4% after the 2nd dose preventing symptomatic COVID-19; 100% effective in preventing severe COVID-19.	2–8 °C for 6 months	Fatigue, myalgia, headache, feverishness or chills, and fever higher than 38 °C	[198,199]

Vaccine Type	Name	Characterization	Company	Vaccine Efficacy	Storage	Systemic Reactogenicity	References
Viral Vector Vaccines	Ad26.COV2.S	Recombinant replication-incompetent human viral vector encoding a full-length, stabilized SARS-CoV-2 S protein	Janssen Pharmaceutical Companies (Johnson & Johnson)	64% efficacy against moderate-to-severe COVID-19; 81.7% efficacy against severe COVID-19	Stored at 2 to 8 °C for less than 6 months; more than 6 months −20 °C	Injection site pain, headache, fatigue, myalgia, nausea, venous thromboembolic events, seizures, and tinnitus	[188,200]
	Ad5-nCoV	Replication-defective adenovirus type-5 vectored vaccine that encodes the SARS-CoV-2 spike protein	CanSinoBIO	65 to 69% efficacy against symptomatic COVID-19; 90 to 95% efficacy against severe COVID-19	Stored at 2–8 °C	Fever, fatigue, and headache	[201]
	Sputnik V	Full-length SARS-CoV-2 glycoprotein S carried by adenoviral vector	The Gamaleya National Center	91.6% efficacy against symptomatic COVID-19; 100% effective in preventing severe COVID-19.	Stored at 2 to 8 °C for less than 6 months; −18 °C in liquid form.	Mild pain at the injection site, fever, headache, fatigue, and muscle aches	[199]

The development of chemically inactivated viruses increased the stability of this vaccination strategy to deliver native antigenic epitopes. This approach was already used against influenza virus and poliovirus [202].

Table 3 summarizes the characteristics of these viruses, some of which were approved only because of emergency, given the scarce information available on their efficacy [188,203–205].

Table 3. Summary of COVID-19 inactivated vaccines that were used globally.

Vaccine Type	Name	Characterization	Company	Vaccine Efficacy	Storage	Systemic Reactogenicity	References
Inactivated Vaccines	BBIBP-CorV	Inactivated HB02 strain with aluminum hydroxide adjuvant	Sinopharm, Beijing Institute of Biological Products	78.1% efficacy against symptomatic COVID-19; 90 to 95% efficacy against severe COVID-19	2–8 °C (unknown lifespan)	Pain, fatigue, headache, lethargy, and tenderness.	[188,206,207]
	CoronaVac	Inactivated CN02 strain with aluminum hydroxide adjuvant	Sinovac Biotech	Variable efficacy when comparing different countries (50.7–83.5%); 100% efficacy against severe COVID-19	2–8 °C (unknown lifespan)	Injection site pain and fatigue are the most common events; adverse events include an allergic reaction	[188,208–211]

The existence of specific pathologic conditions might have affected the eligibility of certain individuals for specific COVID-19 vaccines, due to their efficacy in combating symptom severity. Individuals with a history of vaccine-induced thrombotic thrombocytopenia (VITT) or capillary leak syndrome were advised not to be administered adenoviral vectors, as they could possibly potentiate the outcomes of those conditions [212,213]. Rare contraindications have also been described for mRNA-based vaccines, such as an increased risk of acute myocarditis. When this possibility was detected, those individuals were recommended to defer further doses [214]. The use of polysorbate 80 in adenoviral vector vaccines and of polyethylene glycol (PEG) or tromethamine in mRNA vaccines raised initial concerns regarding the possibility of developing severe allergic reactions. However, these types of secondary effects were uncommon [215]. A certain degree of variability in vaccine effectiveness was observed in high-risk patients, such as immunocompromised individuals. This group included cancer patients, organ transplant recipients, and individuals prescribed with immunosuppressive therapies, to whom additional doses or boosters were recommended. Guidelines containing specific considerations, like delaying vaccination in patients undergoing hematopoietic stem cell transplantation, or prioritizing individuals suffering from kidney or liver disease, who were, respectively, on dialysis or receiving immunosuppressive treatment, were elaborated [214].

9. Vaccine Inequity Distribution in Africa

Contrarily to the multiple vaccination rounds that developed countries benefited from, most African nations did not reach complete vaccination coverage (Figure 2) [216]. Several aspects contributed to the vaccine distribution inequity, including the poor social services taking care of vaccine storage, the conflicts and wars occurring in different countries, the internal migration issues and environmental degradation that hindered vaccine transportation, and a weak governance, violating human rights [3]. Many African countries also lacked the logistics necessary to receive and administer vaccines against SARS-CoV-2, some of which required low-temperature storage and efficient energy and power to maintain freezer functioning. The level of medical preparedness was a challenge. Contrarily to developed countries, the number of health care professionals able to plan, supervise, and follow vaccination procedures was low [3]. This hindered training new nurses and physicians, as the scarce qualified personnel were occupied with saving lives. Insufficient investment, even related to basic equipment and hospital beds, increased the vulnerability of Africa to COVID-19. However, the assumption that most SARS-CoV-2 infections in Africa were asymptomatic or associated with mild clinical symptoms contributed to the decision to regard the continent as a non-priority [216]. The disparity in vaccine distribution, as shown in the figure below, reflected the economic power of many countries and should have raised ethical concerns.
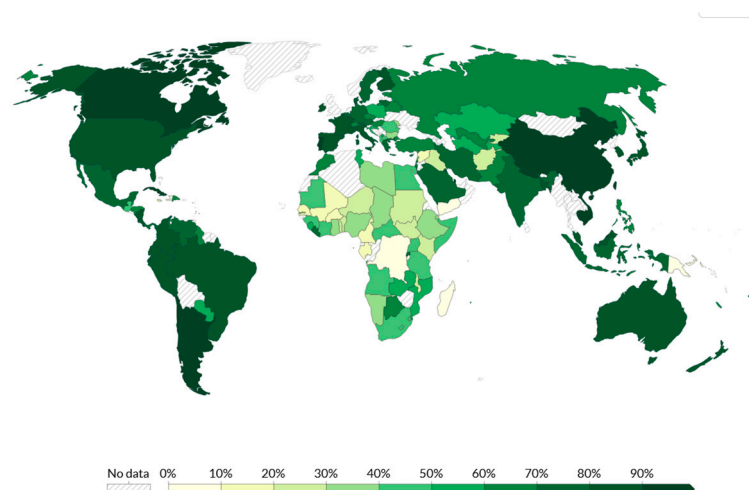

Figure 2. Share of people who received at least one dose of COVID-19 vaccine, up to 15 February 2023. The vaccine coverage was calculated according to the total number of people who received at least one vaccine dose, divided by the total population of the country [217].

In Africa, vaccination programs began on 1 March 2021. The COVAX Facility, co-led by the Coalition for Epidemic Preparedness Innovations (CEPI), Gavi, the Vaccine Alliance, and WHO, secured around 2 billion doses. Vaccines were distributed by the end of the year [218,219], through the cooperation of the Africa Centers for Disease Control and Prevention, the African Union, and the WHO Regional Office for Africa. One of the biggest successes of this partnership was the acquisition of 400 million doses of the Johnson & Johnson single-dose vaccine before the end of 2022 [216]. The AstraZeneca vaccine was approved on 15 February 2021 [220] and had great repercussions in the continent due to its cost-effectiveness, ease of storage, and transportation [3]. It is therefore fair to highlight that it contributed to increasing the vaccination rate in Africa. The International Rescue Committee (IRC) estimated that the extra doses in the US, UK, and EU could have vaccinated individuals over 16 years old in the 20 countries most at risk of humanitarian disaster [221]. However, the multiple waves of COVID-19 reduced donations and caused vaccine shortage. On 19 March 2023, the African continent registered over 55 COVID-19 vaccine doses administered per 100 people, which was significantly lower when compared

to the global average of over 167 doses per 100 people [222]. According to WHO, more than 1 billion doses have been administered in Africa, with 61% of them coming from COVAX, 27% from bilateral agreements, and 11% from the African Union's African Vaccine Acquisition Trust (AVAT). The COVID-19 vaccines used in Africa include Janssen (35%), Pfizer/BioNTech (19%), AstraZeneca (15%), Sinopharm (13%), Sinovac (7%), Moderna (5%), and others (7%) [223]. So far, the African continent has achieved 36.7% coverage of COVID-19 vaccination among its population, which is significantly lower than the global coverage of 69.7% [222,223]. Sierra Leone and Botswana showed the highest level of immunization, reaching 96%, followed by Tunisia (94%) and Eswatini (93%). Conversely, Burundi, Namibia, and the Republic of Congo presented the lowest vaccination coverage, with 4%, 25%, and 26%, respectively. Eritrea is yet to start its COVID-19 vaccination campaign [223], as vaccine hesitancy in sub-Saharan Africa slowed the inoculation rate of COVID-19 vaccines. Some countries refused to participate in the COVAX free vaccine program or delayed vaccination programs due to anti-vaccine sentiments and religious beliefs [224]. Some donated vaccines with a short shelf life rapidly expired [225,226]. Yet, Africa is still vulnerable to new and more transmissible variants of SARS-CoV-2 that may require country-specific solutions [13,221]. The need for African countries to invest in medical science, so as to reduce scientific dependence and assistance from developed nations [3], led several agreements to share vaccine technology, as proposed by Moderna, WHO, BioNTech, and Afrigen Biologics and Vaccines in South Africa [227,228]. The manufacturing capacity was already assessed in Tunisia, Senegal, Egypt, Ethiopia, and South Africa. However, commercial capabilities require further development, given the need to reinforce business planning and market potential, since products produced in many African countries are not accepted in developed regions, as experienced by Rwanda. Whether lucrative markets and parallel importation may be the cause of competing conflicts, to overcome healthcare inequality, multilateral collaborations are required. Sustainable and innovative solutions are needed to overcome disease outbreaks [216], which include empowering the continent to accelerate vaccine manufacturing. Speeding up and encouraging local production, vaccines can be supplied in a timely manner, contributing to removing some of the inequities in the provision of essential health products [229]. In view of the creation of new expertise, this action will foster global collaborative research, which might also aid the discovery of therapeutic treatments better adjusted to the genetics of African individuals, while investigating the consequences of COVID-19 on diseases that are prevalent in the continent. Many pathologies were neglected during the pandemic and now are reemerging, such as measles in the Democratic Republic of Congo [230]. The decreased number of awareness campaigns [231] led to the false perception that the morbidity and mortality of certain pathologies were reduced, as was the case for HIV, cardiovascular diseases, and cervical cancers in Northern Ethiopia [232]. Blood bank services and malaria testing also decreased in Rwanda by almost 200%. Conversely, neonatal death dramatically increased in South Africa, as most personnel were occupied in saving the population from COVID-19 [233].

Finally, it is also worth mentioning that the impact of COVID-19 in Africa extended beyond public health, affecting social and economic aspects. Increased anxiety, social isolation, and stress characterized the pandemic period [3], potentially contributing to enhance domestic violence. Tunisia (43%), Somalia (50%), and South Africa (69%) registered the highest increases [234,235]. A higher risk of child labor and exploitation was also detected [236], possibly considered as a way for families to overcome the economic pressure imposed by the lockdown. These aspects contributed to a rise in the incidence of mental and psychosocial disorders [3], enhancing the vulnerability of this continent.

10. Conclusions

Few studies have assessed the impact of COVID-19 in Africa, despite the contribution of the continent in supporting genomic sequencing and surveillance programs [237] against the new variants of concern [238]. Contrary to expectations, Africa represented a success story. A lower incidence, prevalence, and mortality characterized the pandemic. Official

reports revealed those rates to be lower than one tenth the global COVID-19 cumulative counts [22,217]. Among the possible explanations, youthfulness stood out. The memory phenotype, acquired with exposure to helmites, malaria, tuberculosis, polio, and measles, among others, could also be highlighted as being protective against SARS-CoV-2. Actually, trained immunity was the underlying cause of BCG vaccine testing against COVID-19, the results of which were ultimately inconclusive [239]. Important contributors to reducing the severity of COVID-19 symptoms in Africa also included environmental parameters, despite the need for more studies to understand the dynamics of SARS-CoV-2 infection and its seasonal transmissibility. Further investigations are required to shed light on the peculiar dynamics of COVID-19 in Africa. The consequences of this pandemic on the socioeconomic development of the continent need also to be evaluated, as it affected the accomplishment of specific country goals. It is important to highlight that a collaborative effort is essential to empower health science research in Africa. The sharing and transfer of knowledge is a major step towards the definition of prepared healthcare plans, based on a more holistic vision of a multidisciplinary scientific strategy, turning developmental willingness into action.

Author Contributions: Conceptualization, R.G. and A.C.P.; writing—original draft preparation, R.G. and A.C.P.; writing—review and editing, R.G., A.C.P. and I.S.L. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest: The authors declare no conflicts of interest.

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