COVID-19 in Africa: What else?

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The emergence in December 2019 in Wuhan, China of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been followed by a global pandemic of coronavirus disease 2019 (COVID-19). The disease ranges from asymptomatic infection to acute respiratory distress syndrome with multisystem involvement, particularly in older individuals and individuals with co-morbidities [1]. Specific clinical signs have also been described, such as anosmia and dysgeusia [2], and the so-called happy hypoxemia, where there is a disconnection at rest between profound hypoxemia and the absence of proportional signs of respiratory distress [3]. The origin of SARS-CoV-2 is still debated, but COVID-19 has spread rapidly in 2020, resulting in considerable unexpected mortality in Europe and America. As of December 14, 2020, there have been over 72.3 million confirmed cases of COVID-19 globally, including 1.61 million confirmed deaths [4]. As of June 7, 2021, these data were 173.3 and 3.7 million, respectively [4].

Interestingly, in May 2020, the WHO predicted that COVID-19 would take a heavy toll in Africa, with an estimation of 37 million symptomatic cases and around 150,000 deaths for 2020 [5], in relation with the poor ranking of African countries on the United Nations (UN) Development Program's Human Development Index. Another report by the UN Economic Commission for Africa even predicted in April that, of the 1.2 billion African population, 300,000 deaths might occur [6]. However, 10 months after the first cases in Africa were detected in Egypt in mid-February 2020, prevalence and mortality was still low. Mid-December 2020, there had been slightly over 2.38 million confirmed cases, with 56,337 deaths reported [7]. As of this writing early June 2021, with a total of 4.9 million cases and 132,425 deaths, and even after news outbreaks related to emerging SARS-Cov2 variants, we are still below the predictions [7].

Africa cannot be evaluated as a homogeneous territory, and it is critical to evaluate each country independently, with enough data to describe and understand the severity of the pandemic. Besides the observed case-fatality ratio (number of deaths / number of confirmed

cases), mortality (number of deaths / 100,000 population) is probably the most significant way to measure the burden of COVID-19, as it does not depend on the number of people tested and the testing capacities [8].

In our African countries, mortality has remained at the end of 2020 at a low level, as follows: Algeria (6.12/100,000), Gabon (2.97/100,000), Mali (0.99), Mauritania (5.05/100,000), Morocco (18.29/100,000), Niger (0.36/100,000), Republic of the Congo (6.71/100,000), the Democratic Republic of Congo (0.12/100,000) and Senegal (2.2/100,000). Much higher mortalities have been reported in Western countries such as Belgium (155.77/100,000), the UK (96.44/100,000), France (86.09/100,000), or the USA (91.03/100,000) as examples (for an update and other countries, see ref. 8).

One could say that mortality tends to be higher in older populations, as the median age of Africa is 19.7 (compared to 42.5 in Europe and 38.6 in northern America). However, high mortality has also been reported in other countries on the continent, mainly South Africa (33.08, where the median age is about 27 years). Also, the lack of laboratory facilities to confirm deaths related to COVID-19 cases must be taken into consideration. While South Africa is one of the countries with the best capacities, laboratory testing capacity has increased in other countries, such as Senegal, Algeria and Morocco, as well as in our other countries, such as the Democratic Republic of Congo, which also benefited from previous initiatives to address Ebola [9].

Interestingly, deaths emerged rapidly in some African countries but remained low after the first 150 days, such as in Algeria, although not in South Africa. In other African countries, the dynamic was slower from the beginning [9]. Other factors that might have influenced the introduction, spread and dynamic of COVID-19 in Africa have been discussed elsewhere by some of us [9].

In August 2020, factors which may explain the dampened course of COVID-19 in Africa were discussed in *Science*, ranging from genetic characteristics to immunological

factors and even microbiota [10]. In September 2020, scientists from South Africa reviewed the prospects for SARS-Cov-2 in Africa in *Nature Reviews Microbiology* [11]. As infectious disease and microbiology experts, all involved in the COVID 19 pandemic response in Africa, we want to highlight here another issue not discussed in previous papers (i.e., the impact of chloroquine derivative large scale implementation with or without azithromycin on COVID-19 mortality).

After the first Chinese publications about the antiviral effects of chloroquine (CQ) and its derivatives against SARS-COV2 [12, 13] and a preliminary trial in France [14], many African countries adopted CQ or hydroxychloroquine (HCQ) with or without azithromycin (AZ) to treat presumptive or confirmed COVID-19 cases [15, 16]. This, despite the WHO position [17] and other published or retracted studies claiming that this regimen would not be effective or toxic [18, 19].

More evidence came with the demonstration of a synergistic effect in vitro of the HCQ-AZ combination on SARS-CoV-2 at concentrations compatible with that obtained in the human lung [20] and from observational studies with thousands of cases [21]. In addition, both HCQ and AZ are immunomodulators, which may prevent the “cytokine storm” of COVID 19 [22,23]. In the context of Covid-associated pulmonary embolism, it is important to highlight that i*n vitro* and animal models demonstrated that HCQ had several antithrombotic effects [24, 25]. Also, several clinical studies have underlined the benefit of HCQ for thrombosis prevention in antiphospholipid syndrome, of interest in the context of COVID-19, which induces coagulopathy [26, 27, 28]. Finally, HCQ-AZ has been associated with a reduction in viral shedding, with potential public health effects by reducing the duration of contagiousness [21].

By the end of 2020, while in several African countries a pragmatic, safe use of CQ or HCQ with or without AZ had prevailed, Western countries were still awaiting the results of clinical trials to define their strategy, worrying about hypothetical side effects of HCQ-AZ, which has been used for decades, or are promoting other treatments (with no demonstrated efficacy) or

standard care only, which may be limited when people are asked to remain at home by health authorities. Our therapeutic options have recently been buttressed with the description of 3,737 non-selected COVID 19 patients (including a control group of 618 patients) which demonstrated that receiving HCQ-AZ ≥ 3 days halved the risk of death, divided by 5 the risk of transfer to the intensive care unit, and very significantly reduced the duration of viral shedding; the CFR (case fatality rate) was 0.5% among those who received HCQ-AZ ≥ 3 days. In this study, the risk of confounding associated with age, comorbidities and severity of the disease was controlled by multivariable analyses and propensity score matching approaches [21].

Early care and early treatment remain essential [29, 30]. The dogma about the need randomized controlled trials (RCTs) to support therapeutic choice and public health decision is an issue. However, a Cochrane Library publication stated that observational studies and randomized controlled trials (RCTs) give the same results: "*on average, there is little evidence for significant effect estimate differences between observational studies and RCTs, regardless of specific observational study design, heterogeneity, or inclusion of studies of pharmacological interventions*." [31].

Regarding Africa, a retrospective study in Ghana AZ+CQ or HCQ only as a therapy for managing COVID-19 patients was shown to shorten the duration of hospitalization [32]. Data from Senegal have been also recently reported [33]. By June 2021, more than 300 studies had been published concerning CQ or HCQ, including about 220 peer reviewed, and about 250 comparing treatment and control groups [34]. Most of them are observational studies reporting that early treatment shows positive results, whereas it is not effective when used very late and/or with high dosage over a long period [34].

Regarding the use of HCQ with or without AZ, a meta-analysis has shown as soon as June, 2020, that results from clinical studies differed from those obtained from the analyses of electronic record files [35]. Big data observational studies were associated with conflicts of interest, lack of treatment dosage and duration, and absence of a favorable outcome. Clinical studies were

associated with favorable outcomes and details on therapy. Among clinical studies, three of four RCTs reported a significant beneficial effect for HCQ-AZ. Among clinical studies, a significant beneficial summary effect was observed for duration of cough, duration of fever, clinical cure, death and viral shedding [35].

To date, there is no other accessible therapeutic alternative in Africa with the same evidence. As said above, it is clear to us that treatment must be initiated as early as possible, and that access to care, oxygen, physicians and prevention of pulmonary embolism is also critical for COVID 19 patients [1].

Of course, in addition to the widespread cost-effective use of CQ, HCQ or HCQ-AZ to treat Covid19, other parameters are probably involved of some African countries. Some countries Peru have a high mortality rate, although HCQ has been used there at least within other options for the treatment of COVID-19 patients [36]. In addition to factors discussed in [10] and herein, other factors, such as blood type [37], SARS-CoV-2 diversity [38, 39], climate [40], and prevalence of obesity among the population [41], have to be assessed in order to provide more insights on COVID-19 epidemiological patterns in Africa. The age structure of the population of our countries may help explain differences in fatality rates across countries better than the mean age [40, 42]. As reported by De Larochelambert, countries that already experienced a stagnation or regression of life expectancy, with high income and non-communicable diseases rates, "*had the highest price to pay*" during this outbreak [40].

However, the use of HCQ-AZ for COVID-19 treatment and has resulted in political issues and academic discord [43]. Passionate debates have occurred in the media and scientific journals about the possible toxicity of CQ or HCQ. This, seen from an African perspective, where billions of doses have been dispensed in the past century, speaks volumes about the real safety of these drugs.

In contrast to our colleagues from Cape Town, South Africa [11], where neither CQ nor HCQ is recommended, and where the mortality seems higher than in our African countries, we

think that there are more data available to discuss the potential role of the HCQ derivative. It has been fascinating to note that in a recent review published in Nature [44] about potential SARS-Cov-2 antiviral drugs, the supplementary material must be carefully reviewed to learn that hydroxychloroquine was one of the most active drugs, as this had been forgotten in the text and the summary.

Interestingly, we wrote letters to the editors of Science and Nature Microbiology Reviews to comment on the review listed above [10, 11], and we included part of thoughts presented herein. Both letters were immediately rejected, one after the other, because "*it should be better placed elsewhere*" or "*more primary population-based studies that explore hydroxychloroquine use with prevalence and severity of COVID-19 in Africa are needed before we would publish an article dedicated to this topic*". To date, most of the countries with the highest mortality from COVID-19 include the countries where the most negative media noise about CQ, HCQ or HCQ-AZ has been made, i.e. Western Europe and part of the United States [8]. Also, other cost effective repurposed drugs, such as ivermectin might by of interest for treating COVID-19 patients [45].

Nobody knows how things will turn out in Africa regarding the consequences of the pandemic, including the consequences of the emergence and spread of new variants [45]. Anyway, although the link between the widespread cost-effective use of CQ, HCQ or HCQ-AZ and the evolution of the COVID-19 pandemic evolution in Africa in 2020 and early 2021 has not been yet demonstrated with certainty, it at least deserves to be discussed.

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