COVID-19 in Africa: What else?

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40 **Abstract:**

41 SARS-CoV-2 has spread rapidly in 2020, resulting in considerable unexpected mortality in

42 Europe and America. However, 9 months after the first cases were detected in Africa,

43 prevalence and mortality are still low in many countries of the continent, far below

44 predictions. Although some factors that may explain the dampened course of COVID-19 in

45 Africa have been discussed, we highlight here the potential role of the chloroquine derivative

46 large-scale implementation, with or without azithromycin.

47   The emergence in December 2019 in Wuhan, China of severe acute respiratory syndrome

48   coronavirus 2 (SARS-CoV-2) has been followed by a global pandemic of coronavirus disease

49   2019 (COVID-19). The disease ranges from asymptomatic infection to acute respiratory

50   distress syndrome with multisystem involvement, particularly in older individuals and

51   individuals with co-morbidities (1). Specific clinical signs have also been described, such as

52   anosmia and dysgeusia (2), and the so-called happy hypoxemia, where there is a

53   disconnection at rest between profound hypoxemia and the absence of proportional signs of

54   respiratory distress (3). The origin of SARS-CoV-2 is still debated, but COVID-19 has spread

55   rapidly in 2020, resulting in considerable unexpected mortality in Europe and America. As of

56   December 14, 2020, there have been over 72.3 million confirmed cases of COVID-19

57   globally, including 1.61 million confirmed deaths (4).

58   **Epidemiology**

59   Interestingly, in May 2020, the WHO predicted that COVID-19 would take a heavy

60   toll in Africa, with an estimation of 37 million symptomatic cases and around 150,000 deaths

61   (5), in relation with the poor ranking of African countries on the United Nations (UN)

62   Development Program's Human Development Index. Another report by the UN Economic

63   Commission for Africa even predicted in April that, of the 1.2 billion African population,

64   300,000 deaths might occur (6). However, 10 months after the first cases in Africa were

65   detected in Egypt in mid-February, prevalence and mortality are still low. As of this writing

66   mid-December 2020, there have been slightly over 2.38 million confirmed cases, with 56,337

67   deaths reported (7), far below the predictions.

68   Africa cannot be evaluated as a homogeneous territory, and it is critical to evaluate

69   each country independently, with enough data to describe and understand the severity of the

70   pandemic. Besides the observed case-fatality ratio (number of deaths / number of confirmed

71 cases), mortality (number of deaths / 100,000 population) is probably the most significant way

72 to measure the burden of COVID-19, as it does not depend on the number of people tested

73 and the testing capacities (8).

74   In our African countries, mortality has remained to date at a low level, as follows: Algeria

75 (6.12/100,000), Gabon (2.97/100,000), Mali (0.99), Mauritania (5.05/100,000), Morocco

76 (18.29/100,000), Niger (0.36/100,000), Republic of the Congo (6.71/100,000), the Democratic

77 Republic of Congo (0.12/100,000) and Senegal (2.2/100,000). Much higher mortalities have been

78 reported in Western countries such as Belgium (155.77/100,000), the UK (96.44/100,000), France

79 (86.09/100,000), or the USA (91.03/100,000) as examples (for an update and other countries, see

80 ref. 8). One can say that mortality tends to be higher in older populations, as the median age of

81 Africa is 19.7 (compared to 42.5 in Europe and 38.6 in northern America). However, high

82 mortality has also been reported in other countries on the continent, mainly South Africa (33.08,

83 where the median age is about 27 years). Also, the lack of laboratory facilities to confirm deaths

84 related to COVID-19 cases must be taken into consideration. While South Africa is one of the

85 countries with the best capacities, laboratory testing capacity has increased in other countries, such

86 as Senegal, Algeria and Morocco, as well as in our other countries, such as the Democratic

87 Republic of Congo, which also benefited from previous initiatives to address Ebola (9).

88   Interestingly, deaths emerged rapidly in some African countries but remained low after the

89 first 150 days, such as in Algeria, although not in South Africa. In other African countries, the

90 dynamic was slower from the beginning (9). Other factors that might have influenced the

91 introduction, spread and dynamic of COVID-19 in Africa have been discussed elsewhere by some

92 of us (9).

93   In August 2020, factors which may explain the dampened course of COVID-19 in Africa

94 were discussed in *Science*, ranging from genetic characteristics to immunological factors and even

95 microbiota [10]. In September 2020, scientists from South Africa reviewed the prospects for

96   SARS-Cov-2 in Africa in *Nature Reviews Microbiology* [11]. As infectious disease and

97   microbiology experts, all involved in the COVID 19 pandemic response in Africa, we want to

98   highlight here another issue not discussed in previous papers (i.e., the impact of chloroquine

99   derivative large scale implementation with or without azithromycin on COVID-19 mortality).

100

101   **Hydroxychloroquine and azithromycin**

102   After the first Chinese publications about the antiviral effects of chloroquine (CQ) and its

103   derivatives against SARS-COV2 (12, 13) and a preliminary trial in France (14), many African

104   countries adopted CQ or hydroxychloroquine (HCQ) with or without azithromycin (AZ) to treat

105   presumptive or confirmed COVID-19 cases (15, 16). This, despite the WHO position [17] and

106   other published or retracted studies claiming that this regimen would not be effective or toxic (18,

107   19).

108   More evidence came with the demonstration of a synergistic effect in vitro of the HCQ-AZ

109   combination on SARS-CoV-2 at concentrations compatible with that obtained in the human lung

110   [20] and from observational studies with thousands of cases [21]. In addition, both HCQ and AZ

111   are immunomodulators, which may prevent the "cytokine storm" of COVID 19 [22,23]. In the

112   context of Covid-associated pulmonary embolism, it is important to highlight that i*n vitro* and

113   animal models demonstrated that HCQ had several antithrombotic effects [24, 25]. Also, several

114   clinical studies have underlined the benefit of HCQ for thrombosis prevention in antiphospholipid

115   syndrome, of interest in the context of COVID-19, which induces coagulopathy (26, 27, 28).

116   Finally, HCQ-AZ has been associated with a reduction in viral shedding, with potential public

117   health effects by reducing the duration of contagiousness [21].

118   While in several African countries a pragmatic, safe use of CQ or HCQ with or without AZ

119   has prevailed, Western countries are still awaiting the results of clinical trials to define their

120   strategy, worrying about hypothetical side effects of HCQ-AZ, which has been used for decades,

121   or are promoting other treatments (with no demonstrated efficacy) or standard care only, which

122   may be limited when people are asked to remain at home by health authorities. Our therapeutic

123   options have recently been buttressed with the description of 3,737 non-selected COVID 19

124   patients (including a control group of 618 patients) which demonstrated that receiving HCQ-AZ $\geq$

125   3 days halved the risk of death, divided by 5 the risk of transfer to the intensive care unit, and

126   very significantly reduced the duration of viral shedding; the CFR (case fatality rate) was 0.5%

127   among those who received HCQ-AZ $\geq$ 3 days. In this study, the risk of confounding associated

128   with age, comorbidities and severity of the disease was controlled by multivariable analyses and

129   propensity score matching approaches (21).

130   Currently, more than 160 studies, including about 100 peer reviewed, have been published

131   concerning CQ or HCQ (30, 31, 32); most of them are observational studies. A Cochrane Library

132   publication stated that observational studies and randomized controlled trials (RCTs) give the

133   same results: "*on average, there is little evidence for significant effect estimate differences*

134   *between observational studies and RCTs, regardless of specific observational study design,*

135   *heterogeneity, or inclusion of studies of pharmacological interventions*." (33).

136   Regarding the use of hydroxychloroquine with or without azithromycin, a recent meta-

137   analysis has shown that results from clinical studies differed from those obtained from the

138   analyses of electronic record files (34). Big data observational studies were associated with

139   conflicts of interest, lack of treatment dosage and duration, and absence of a favorable outcome.

140   Clinical studies were associated with favorable outcomes and details on therapy. Among clinical

141   studies, three of four RCTs reported a significant beneficial effect for HCQ-AZ. Among clinical

142   studies, a significant beneficial summary effect was observed for duration of cough, duration of

143   fever, clinical cure, death and viral shedding. For an update of our metanalysis, see the link in

144   reference 35. To date, there is no other accessible therapeutic alternative with the same evidence.

145   Of course, other parameters are probably involved. Peru has a high mortality rate

146   (114.24/100,000), although HCQ has been used there for the treatment of COVID-19 patients

147   (36). However, it is clear to us that treatment must be initiated as early as possible, and that access

148   to care, oxygen, physicians and prevention of pulmonary embolism is also critical for COVID 19

149   patients.

150

151   **Conclusion**

152   In addition to factors discussed in (10) and herein, other factors, such as blood type (37) and

153   SARS-CoV-2 diversity have to be assessed in order to provide more insights on COVID-19

154   epidemiological patterns in Africa (38). The use of HCQ-AZ remains controversial and has

155   resulted in political issues and academic discord (39, 40). Passionate debates have occurred in the

156   media and scientific journals about the possible toxicity of CQ or HCQ. This, seen from an

157   African perspective, where billions of doses have been dispensed in the past century, speaks

158   volumes about the real safety of these drugs. In contrast to our colleagues from Cape Town, South

159   Africa (11), where neither CQ nor HCQ is recommended, and where the mortality seems higher

160   than in our African countries, we think that there are more data available to discuss the potential

161   role of the HCQ derivative. It has been fascinating to note that in a recent review published in

162   Nature (40) about potential SARS-Cov-2 antiviral drugs, the supplementary material must be

163   carefully reviewed to learn that hydroxychloroquine was one of the most active drugs, as this had

164   been forgotten in the text and the summary. Interestingly, we wrote letters to the editors of Science

165   and Nature Microbiology Reviews to comment on the review listed above, and we included part of

166   the material presented herein. Both letters were immediately rejected, one after the other, because

167   "*it should be better placed elsewhere*" or "*more primary population-based studies that explore*

168   *hydroxychloroquine use with prevalence and severity of COVID-19 in Africa are needed before*

169   *we would publish an article dedicated to this topic*". To date, most of the countries with the

170   highest mortality from COVID-19 include the countries where the most negative media noise

171   about CQ, HCQ or HCQ-AZ has been made, i.e. Western Europe and part of the United States (8)

172   Although the link between the widespread cost-effective use of CQ, HCQ or HCQ-AZ and the

173   evolution of the COVID-19 pandemic evolution in Africa has not been yet demonstrated with

174   certainty, it at least deserves to be discussed.

175

176   **Conflict of Interest and Financial Disclosures:**

177   The authors have no financial or non-financial actual or potential conflicts of interest.

178

179   **Aknowledgments**

180   This manuscript has been edited by a native English speaker.
181

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