COVID-19 in Africa: What else?

Cheikh Sokhna1, Souleymane Brah2, Abdoulaye Djimde3, Nadjet Mouffok4, Majida Zahraoui5, Ali Ould Mohamed Salem Boukhary6, Idir Bitam7, Badara Cisse8, Mahamadou Ali Thera3, Jean-Bernard Lekana-Douki9, Eric Adehossi10, Moussa Seydi11, Jean Akiana12, Jaafar Heikel5, Jean-Christophe Lagier14,15, Souleymane Mboup8, Jean-Jacques Mouyembe-Tamfum16, Philippe Parola14,17 *

1 VITROME, Campus International IRD-UCAD, Dakar, Senegal
2 Service de Médecine Interne, Hôpital Général de Référence, Niamey, Niger
3 Malaria Research and Training Center, University of Science, Techniques and Technologies of Bamako, Bamako, Mali
4 Service des Maladies Infectieuses, Centre Hospitalier Universitaire, Oran, Algeria
5 Service de Médecine Interne, Clinique De Vinci, Casablanca, Morocco
6 Université de Nouakchott Al Aasriya, Nouakchott, Mauritania
7 École Supérieure en Sciences de l’Aliment et des Industries Agroalimentaire, Direction générale de la recherche scientifique et développement technologique, Ministère de l’enseignement supérieur et de la recherche scientifique, Alger, Algeria
8 Institut de recherche en Santé, de Surveillance Epidemiologique et de Formation (IRESSEF), Dakar, Senegal
9 Département de Parasitologie-Mycologie, Université des Sciences de la Santé (USS) Libreville, UNEEREP-CIRMF, Franceville, Gabon.
10 Université Abdou Moumouni, Niamey, Niger
11 Service de Maladies Infectieuses et Tropicale, Centre Hospitalier Universitaire de Fann, Université Cheikh Anta Diop, Dakar, Senegal.
12 Faculté des Sciences et Techniques/Université Marien NGOUABI de Brazzaville, République du Congo
13 University Hospital Institute IHU-Méditerranée Infection, Marseille, France
14 Aix Marseille Univ, IRD, AP-HM, MEPHI, Marseille, France
15 Département de Microbiologie, Faculté de Médecine, Université de Kinshasa, Kinshasa, Democratic Republic of Congo
16 Aix Marseille Univ, IRD, AP-HM, SSA, VITROME, Marseille, France

Corresponding Author:
Philippe Parola
Email: philippe.parola@univ-amu.fr
Phone: +33413732401
Abstract:

SARS-CoV-2 has spread rapidly in 2020, resulting in considerable unexpected mortality in Europe and America. However, 9 months after the first cases were detected in Africa, prevalence and mortality are still low in many countries of the continent, far below predictions. Although some factors that may explain the dampened course of COVID-19 in Africa have been discussed, we highlight here the potential role of the chloroquine derivative large-scale implementation, with or without azithromycin.
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).

Epidemiology

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 (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, prevalence and mortality are still low. As of this writing mid-December 2020, there have been slightly over 2.38 million confirmed cases, with 56,337 deaths reported (7), far below the predictions.

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 to date 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 can 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).

**Hydroxychloroquine and azithromycin**

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 in 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].

While in several African countries a pragmatic, safe use of CQ or HCQ with or without AZ has prevailed, Western countries are 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).

Currently, more than 160 studies, including about 100 peer reviewed, have been published
concerning CQ or HCQ (30, 31, 32); most of them are observational studies. 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." (33).

Regarding the use of hydroxychloroquine with or without azithromycin, a recent meta-
analysis has shown that results from clinical studies differed from those obtained from the
analyses of electronic record files (34). 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. For an update of our metanalysis, see the link in
reference 35. To date, there is no other accessible therapeutic alternative with the same evidence.
Of course, other parameters are probably involved. Peru has a high mortality rate
(114.24/100,000), although HCQ has been used there for the treatment of COVID-19 patients
(36). However, it is clear to us that treatment must be initiated as early as possible, and that access
Conclusion

In addition to factors discussed in (10) and herein, other factors, such as blood type (37) and SARS-CoV-2 diversity have to be assessed in order to provide more insights on COVID-19 epidemiological patterns in Africa (38). The use of HCQ-AZ remains controversial and has resulted in political issues and academic discord (39, 40). 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 (40) 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, and we included part of the material 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). Although the link between the widespread cost-effective use of CQ, HCQ or HCQ-AZ and the
The evolution of the COVID-19 pandemic evolution in Africa has not been yet demonstrated with certainty, it at least deserves to be discussed.

**Conflict of Interest and Financial Disclosures:**

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

**Acknowledgments**

This manuscript has been edited by a native English speaker.
References:


4. https://coronavirus.jhu.edu


8. https://coronavirus.jhu.edu/data/mortality


17. WHO. https://www.who.int/publications/m/item/targeted-update-safety-and-efficacy-of-
hydroxychloroquine-or-chloroquine-for-treatment-of-covid-19

18. Mehra MR, Ruschitzka F, Patel AN. Retraction-Hydroxychloroquine or chloroquine with
or without a macrolide for treatment of COVID-19: a multinational registry analysis.

19. Million M, Chaudet H, Raoult D. Hydroxychloroquine Failure: The End does not justify

JM, Colson P, La Scola B, Raoult D. In vitro testing of combined hydroxychloroquine
and azithromycin on SARS-CoV-2 shows synergistic effect. Microb Pathog. 2020

Gaubert JY, Fournier PE, Tissot-Dupont H, Chabrière E, Stein A, Deharo JC, Fenollar F,
Rolain JM, Obadia Y, Jacquier A, La Scola B, Brouqui P, Drancourt M, Parola P, Raoult
D; IHU COVID-19 Task force. Outcomes of 3,737 COVID-19 patients treated with
hydroxychloroquine/azithromycin and other regimens in Marseille, France: A
retrospective analysis. Travel Med Infect Dis. 2020;36:101791. doi:

Immune modulation as a therapeutic option during the SARS-CoV-2 outbreak: the case
for antimalarial aminoquinolines. Front. Immunol. 2020; 11:2159. doi:
10.3389/fimmu.2020.02159

23. Zimmermann P, Ziesenitz VC, Curtis N, Ritz N. The Immunomodulatory effects of
macrolides- A systematic review of the underlying mechanisms. Front Immunol. 2018


32. https://c19study.com


37. Taha SAH, Osman MEM, Abdoelkarim EAA, Holie MAI, Elbasheir MM, Abuzeid NMK, Al-Thobaiti SA, Fadul SB, Konozy EHE. Individuals with a Rh-positive but not Rh-negative blood group are more vulnerable to SARS-CoV-2 infection: demographics and trend study on COVID-19 cases in Sudan. New Microbes New Infect. 2020
308    PMCID: PMC7505818.
309    38. Colson P, Levasseur A, Delerce J, Chaudet H, Brechard L, Bossi V, Ben Khedher M,
310    Fournier PE, Lagier JC, Raoult D. Dramatic increase in SARS-CoV-2 diversity and
311    decrease of mortality rate during the second epidemic in summer in Marseille.
316    Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-
318    Pre-print doi: https://doi.org/10.35088/bjjr-cv47
319    41. Riva L, Yuan S, Yin X, Martin-Sancho L, Matsunaga N, Pache L, Burgstaller-
320    Muehlbacher S, De Jesus PD, Teriete P, Hull MV, Chang MW, Chan JF, Cao J, Poon
322    Rathnasinghe R, Schotsaert M, Miorin L, Dejosez M, Zwaka TP, Sit KY, Martinez-
323    Sobrido L, Liu WC, White KM, Chapman ME, Lendy EK, Glynne RJ, Albrecht R,
325    A, Chatterjee AK, Yuen KY, Chanda SK. Discovery of SARS-CoV-2 antiviral drugs
326    through large-scale compound repurposing. Nature. 2020 Oct;586(7827):113-119. doi:
327    10.1038/s41586-020-2577-1. Epub 2020 Jul 24. PMID: 32707573; PMCID:
328    PMC7603405.