What could explain the late emergence of COVID-19 in Africa?

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Abstract

At the end of November 2019, a novel coronavirus responsible for respiratory tract infections emerged in China. Despite drastic containment measures, this virus, known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), spread in Asia and Europe. The pandemic is ongoing with a particular hotspot in southern Europe and America in spring 2020. Many studies predicted an epidemic in Africa similar to that currently seen in Europe and the USA. However, reported data do not confirm these predictions. Several hypotheses that could explain the later emergence and spread of the coronavirus disease 2019 (COVID-19) pandemic in African countries are being discussed, including the lack of health-care infrastructure capable of clinically detecting and confirming COVID-19 cases, the implementation of social distancing and hygiene, international air traffic flows, the climate, the relatively young and rural population, the genetic polymorphism of the angiotensin-converting enzyme 2 receptor, cross-immunity and the use of antimalarial drugs. © 2020 The Author(s). Published by Elsevier Ltd.

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Introduction

In December 2019, the Chinese health authorities reported the emergence of a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), in Wuhan (China), after clinicians had published that this new Sarbecovirus was causing a disease subsequently named COVID-19 (coronavirus disease 2019) [1,2]. In fact, retrospective studies show that SARS-CoV-2 has already been circulating for several weeks, probably since October 2019, with a case of COVID-19 formally identified on 17 November 2019 [3]. Among 10 237 infected individuals with SARS-CoV-2 included in a nationwide cohort in South Korea (24 January to 9 April 2020), 6350 individuals (62%) were asymptomatic [4]. In another study on 1096 individuals in Kuwait (24 February to 20 April 2020), 46.3% of the infected people were asymptomatic on the sample day [5]. Thirty-five individuals (6.9%) who were initially asymptomatic developed symptoms later [5]. Asymptomatic infection can occur at any age, but had a higher prevalence in patients under 45 years old compared with symptomatic people [6]. In a meta-analysis, the most frequent clinical signs and symptoms reported in symptomatic patients were fever (78.5%), cough (53.8%) and fatigue (25.0%), and 6.8% of the patients were admitted to the intensive care unit and 7.7% died during hospitalization due to complications related to COVID-19 (pneumonia, secondary bacterial infection and respiratory failure) [7].

Because of its high transmission efficiency [8], SARS-CoV-2 spread worldwide, prompting the WHO to declare an international public health emergency on 30 January 2020 [9], and a pandemic on 11 March 2020 [10]. Following the early outbreak in China, COVID-19 spread to other Asian countries and western European countries and then to the USA in Spring 2020 (Fig. 1). COVID-19 later spread to Central and South America, Africa, India and Southeastern Asia. Cities most
affected by COVID-19 are either those with intensive international economic exchanges, such as Hong Kong, Milan, London, Paris, Madrid, and more recently New York, or cities having recently hosted events bringing together many people. It is worth noting that in the ranking of countries that faced the most severe outbreaks, Italy was the first to be very strongly impacted in Europe.

Interestingly, it was reported that the Lombardia region, accounting for the highest number of COVID-19 cases in Italy, is the region with the highest percentage of Chinese residents (23% of its population being composed of Chinese residents) [11]. Although the pandemic has evolved rapidly at the global level (on 23 March 2020, 174 countries and territories had been affected by COVID-19, whereas on 4 June, almost all countries worldwide were involved (Fig. 1)), the African continent has so far reported only a very small number of cases.

As of 4 June 2020, 54 countries are affected in Africa with 150 610 cumulative confirmed cases and 4281 reported deaths [12]. The five most affected African countries are South Africa with 37 525 cases and 792 deaths, Nigeria with 11 166 cases and 315 deaths, Algeria with 9733 cases and 673 deaths, Ghana with 8548 cases and 38 deaths, and Cameroon with 6789 cases and 203 deaths, on June 4, 2020. The first confirmed African cases of SARS-CoV-2 were reported on 14 February 2020 in Egypt for north Africa [13] and on 27 February 2020 in Nigeria for Sub-Saharan Africa [14]. Gilbert et al. estimated the risk of importation of cases of COVID-19 to Africa according to air travel flows from infected provinces of China to Africa and taking into account the African countries’ capacity to detect COVID-19 [15]. The countries at highest importation risk from China were Egypt, Algeria, South Africa, Nigeria, and Ethiopia. Three of these countries (South Africa, Algeria, and Nigeria) are the three most affected countries and Egypt has recorded 28 615 cases and 1088 deaths. Another study predicted a high risk of exposure in countries of small size like Mauritius (1 097 013 estimated cases for 1 265 303 inhabitants; 335 confirmed cases on 4 June 2020) or Equatorial Guinea (819 289 estimated cases for 1 308 974 inhabitants; 1306 confirmed cases on 4 June 2020) [16]. Using a branching process model, Pearson et al. estimated the number of cases of COVID-19 in each African country, and more especially the timing of reporting 10 000 cases for all African countries [17]. For instance, the timing of reporting 10 000 cases was between 11 and 18 April (3836 cases on 4 June 2020) in Senegal, 17 and 23 April (6585 cases on 4 June 2020) in Cameroon, 7 to 21 May (86 cases on 4 June 2020) in Angola and 23 April and 3 May (1486 cases on 4 June 2020) in Ethiopia. The data declared to WHO indicated the spread of COVID-19 in Africa but with lower confirmed cases than expected. We discuss several hypotheses that could explain the later emergence and spread of the COVID-19 pandemic in African countries.

Information gathering regarding COVID-19 cases and deaths

The gathering of available information regarding the number of infected people varies between countries depending on several

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FIG. 1. Confirmed cases of COVID-19 by country (4 June 2020). The colour gradient (dark to light) represents the graduated number of confirmed cases (highest to lowest). The figure was generated by compiling the data on COVID-19 cases on 4 June 2020, in each country worldwide (from Worldometer [124]).
factors. First, screening strategies vary considerably between countries according to the availability of virus-screening assays. For instance, in western countries, some countries (like France) have recommended testing only people with mild to severe symptoms, whereas other countries (like Germany) have adopted an open strategy to detect asymptomatic persons and then isolate positive persons. At the beginning of February 2020, only two countries in Africa (Senegal and South Africa) had laboratories able to carry out RT-PCR tests, the reference standard in COVID-19 testing, in the absence of available and reliable rapid diagnostic tests [18]. Between 2 February and 1 March 2020, the laboratory capacity for testing for SARS-CoV-2 had increased from two to 34 countries [19]. However, on 1 April 2020, South Africa had tested more than 47 000 people, but Zimbabwe had tested only 316 people and Namibia only 306 [20]. The lack of health-care infrastructure capable of clinically detecting and subsequently confirming COVID-19 cases is obviously the most important reason for the relatively low number of confirmed cases in Africa [21]. The most affected country is South Africa with 37 525 cases and 792 deaths (4 June 2020), one of the countries with the best diagnostic capacities with more than 3 million tests performed on 13 August 2020 [22]. However, between 2 February and 15 April 2020, laboratory testing capacity has increased from two countries (South Africa and Senegal) to 44 countries in the WHO African Region [23]. The situation is even more precarious in war zones and the many landlocked zones.

Another possible explanation of the weakness of epidemiological signals regarding COVID-19 in Africa is the hypothesis that epidemiological surveillance cannot be carried out appropriately and that syndromic surveillance is difficult due to confounding factors linked to other respiratory infections. For instance, COVID-19 has been reported in the same areas in Brazil where cases of dengue fever, with similar clinical and laboratory characteristics, have been identified [24].

**Physical distancing and enhanced hygiene**

WHO anticipates a rapid increase in the number of individuals with COVID-19 on the African continent and Africa has responded quickly. African health ministers quickly implemented the Africa Taskforce for Coronavirus Preparedness and Response on 3 February 2020 [25]. Physical distancing and enhanced hygiene are two of the response measures. Lockdown measures, like closing schools, churches, mosques or markets to promote social distancing or shutting down airports, have been rapidly implemented in some African countries [26–28]. However, lockdown and working from home are unlikely to be implementable in many areas of Africa because of a cash economy, daily work requiring physical presence, and electricity or internet inaccessibility [29]. Sanitary measures including access to soap, water and hydroalcoholic gel, are also difficult to set up [30,31]. More than 50% of the population in sub-Saharan Africa was without access to handwashing in 2019 [31]. In three African countries (Nigeria, Ethiopia and Democratic Republic of the Congo), more than 50 million people were estimated to be without handwashing access [31]. Additionally, physical distancing and enhanced hygiene are unlikely to be implementable in refugee camps, shantytowns or overcrowded settings [32–34]. However, several African countries have benefited from previous initiatives to address Ebola [35,36]. For instance, the surveillance structure and screening measures in airports developed for Ebola virus disease became pillars in the COVID-19 response in Uganda [35] and Ebola standard operating procedures were updated for COVID-19 in the Democratic Republic of Congo [36].

**Delay in the dynamic of the COVID-19 epidemic**

The hypothesis of a marked delay of the onset of the epidemic in Africa could be linked to less frequent exchanges between China and Africa (a mono-directional exchanges model where it is especially the Chinese who travel to Africa) than between China and Europe or China and the USA (a bi-directional exchange model). According to air travel flows from infected provinces in China to Africa and the African country’s capacity to detect COVID-19, Gilbert et al. estimated that Egypt, Algeria, South Africa, Nigeria and Ethiopia presented the highest risk of importation of cases of COVID-19 from China [15]. Another study, based on the analysis of 388 327 passengers travelling to 1297 airports, estimated that the risk of transmission to Africa was very low [37]. The only African countries identified as at high risk were Ethiopia (28th) and South Africa (40th). Egypt, Algeria and Nigeria were estimated as at low risk (59th, 88th and 100th, respectively). However, this hypothesis is questionable: the African continent attracted 121 million Chinese visitors in 2017 (a tremendous growth compared with 2005 (31 million)) [38], while according to the China Tourism Academy, about six million Chinese visitors were recorded as travelling to Europe in 2018 and with an 8% increase in the first 6 months of 2019 [39]. But the status of Chinese visitors is different between Europe and Africa. Most Chinese visitors in Europe are either students, tourists or on business trips. In contrast, most Chinese visitors to Africa are construction workers, engineers, translators, or company executives who stay in Africa for a long time [40] and the number...
of Chinese ranged between 1 and 2 million in 2020 [41]. In 2017, Chinese tourists accounted for only 11 million flights for a total of 121 million visitors [42]. The Chinese workers typically fly back to China once or twice a year, and especially for Chinese New Year. In contrast, many Chinese tourists leave China for Europe on vacation days before the Chinese New Year Day. Most of the first COVID-19 cases in Europe have been linked to Chinese tourists or people returning from China [43,44]: on 29 January 2020, two Chinese tourists from Hubei province coming to Italy [45]; on 27 January 2020, a Chinese individual working for a company in Munich who had been in contact with their parents from Wuhan before visiting Germany [46]; on 4 February 2020, a Belgian individual returning from Wuhan [47]; on 27 January 2020, two Chinese tourists coming to England [48]; or on 24 January 2020, a French individual returning from Wuhan and two Chinese tourists from Wuhan [49].

What is interesting is that the majority of the initial cases of COVID-19 in Africa have been linked to European travel rather than China. The first case of SARS-CoV-2 in Nigeria was identified in an Italian citizen on 27 February 2020 [14], in Italian people on 1 March 2020 in South Africa [50], in an Italian citizen on 17 February 2020 in Algeria [51], in a French citizen on 24 February 2020 in Cameroon [52], in a French resident in Dakar returning from France on 26 February 2020 in Senegal [53], in two citizens arrived in Ghana from Norway and Turkey on 12 March 2020 [54], in a Kenyan citizen returning to Kenya from the USA via London on 5 March 2020 [55] and in a Japanese man who travelled from Japan to Burkina Faso before coming to Ethiopia on 13 March 2020 [56]. Among the countries most affected by COVID-19, only the first case in Egypt came from Wuhan [57].

First cases of SARS-CoV-2 were identified preferably in January–February 2020 in Europe and the USA, and in February–March in Africa and Brazil. The dynamic of the expansion of COVID-19-related deaths was different between the countries (Fig. 2). Deaths emerged rapidly in African countries but stayed low after the first 150 days, Logarithmic analysis of the cumulative deaths (Fig. 2c, d) showed that the number of deaths evolved in a similar way in South Africa and Algeria during the first 30 days to what was observed in the USA, Brazil or Europe. The dynamic was slower in Nigeria, Cameroon, Senegal, Ghana, Kenya and Ethiopia than in South Africa or Algeria (Fig. 2d).

Demographic hypothesis

One hypothesis that has been rarely mentioned to explain the weakness of the epidemiological signal in Africa regarding the COVID-19 epidemic (and potentially a delay in its dynamic) is the fact that its population is extremely young. In 2015, 40% of its population was aged 0–14 years and 19% was aged 15–24 years, whereas those aged over 65 years accounted for only 3.5%. The proportion of people over 65 years of age in 2019 was higher in Southeastern Asia (7%), in Central America (7%) and South America (9%) but remained much lower than in Europe (21%) [58]. The relatively young and rural population has certainly limited the spread and severity of COVID-19 in Africa [59]. Yet, there is a consensus to consider that COVID-19 is far less severe in children than in adults, and that in this group, most of them are asymptomatic. For example, in China, in a study conducted on 7736 individuals who had been hospitalized with COVID-19, only 0.9% were younger than 15 years [60]. Disease severity in patients under 15 years of age represented only 0.6% of the total number of cases. Individuals over 65 years of age accounted for 15.1% of the patients and 27.0% of the total severity. In an investigation of 72 314 cases, Wu et al. reported that children under 9 and from 10 to 19 years old represented 1% of the total number of cases, respectively [61]. In a clinical and epidemiological study conducted on 36 children, 28% were asymptomatic versus <5% in adults, 36% showed fever versus 89% in adults, 0% showed severe disease versus 23% in adults [62].

Role of climate

Environmental factors, especially temperature and relative humidity, may influence SARS-CoV-2 transmission [63]. High temperature and high humidity may reduce coronavirus transmission [64], which could explain the relatively low number of confirmed cases in Africa. Around 60% of the world cases occurred in areas where temperature ranged from 5 to 15 °C [65]. The rate of confirmed cases significantly decreased with maximum temperature above 22.5 °C [66]. Mean daily cases and deaths were significantly lower in the hottest countries with highest temperatures reported between 29 December 2019 and 12 May 2020 (26.3 °C; 407.1 daily cases and 17.8 daily deaths) than in the coldest countries with lowest temperatures (6.2 °C; 1876.7 daily cases and 100.4 daily deaths) [67]. The viral transmissibility is estimated by the reproduction number \( R_0 \), which represents the number of people that will be infected by an individual who has an infection. The SARS-CoV-2 \( R_0 \) was >2 for temperatures below 0 °C, decreased to \( R_0 = 1 \) for temperatures increasing from 0 °C to 11 °C, increased to \( R_0 = 1.6 \) for temperatures increasing from 11 °C to 20 °C, and gradually decreased to \( R_0 = 1 \) for temperatures above 20 °C [68]. However, a study carried out in Australia suggested that even with high temperature, COVID-19 could
Another study showed that in Brazil, high temperatures and relative humidity favoured COVID-19 transmission [70]. Genetic polymorphism of angiotensin-converting enzyme 2 (ACE2), the cell entry receptor for SARS-CoV-2, could play a role in SARS-CoV-2 transmission [71,72]. Analyses of different geographical populations demonstrated the existence of at least 32 variants of ACE2 (single mutation, deletion, truncation) [73]. Expression of a specific variant allele in African subpopulations could alter the process of interaction between the viral S protein and the ACE2 receptor on the alveolar cells of the lung. In addition, expression quantitative trait loci variants were reported to regulate the expression of the ACE2 gene. ACE2 gene expression was down-regulated by variants rs11271234 and rs75979613 and up-regulated by the other variants [74–76].

Moreover, the ACE1 gene, an analogue of ACE2, can have insertion (I) or deletion (D) of a 287-bp Alu repeat sequence in intron 16 [77]. Three different genotypes exist: II, ID and DD. The number of patients infected with SARS-CoV-2 and the number of deaths from COVID-19 were negatively associated with the ACE1 II genotype frequency [78]. The European population has a lower ACE1 II genotype frequency and a higher prevalence of infected patients and
mortality due to COVID-19 than the Asian population [78].
These data are consistent with an epidemiological study that
reported a significant positive correlation of the D allele with
SARS-CoV-2 infection prevalence and mortality rate in Asian
population [79]. The DD genotype was also increased in
acute respiratory distress syndrome [80]. Increase of ID
genotype frequency was found to increase recovery rate af-
after COVID-19 [81]. The frequencies of D allele were
different between ethnic groups: it ranged from 72% to 77%
in North African individuals (Moroccans, Egyptians, Algerians,
Tunisians), 59% in West African individuals (Nigerians), 64% to
73% in East African individuals (Sudanese, Somalis), only
14% in South African individuals (Zambians), 29% in Chinese
individuals, 9% in Samoan individuals, and 46% in Caucasian
individuals [82]. For instance, the DD frequency was 43% for
Sudanese individuals [83], 51% for Somali individuals [83],
36% for Burkinabe individuals [84], 34% for South African
individuals [85] and 30% for European individuals [86]. Pro-
spective studies are needed to investigate ACE genotype
frequencies in different world areas and a potential role in
delayed transmission. Moreover, other SARS-CoV-2 re-
cceptors could be involved in COVID-19 cases and mortality
rate, like the transmembrane protease serine 2 (encoded by
TMPRSS2) [87]. TMPRSS2 up-regulating variants were found
at higher frequencies in European and American populations
than in the Asian and African populations, which implies that
these populations might be relatively susceptible to SARS-
CoV-2 infection [87].

FIG. 2. Continued
Cross-immunity to SARS-CoV-2

Protective immune responses to viral infection occur following the combined actions of B cells (humoral immunity) and T cells (cellular immunity). In COVID-19, B cells produce IgM, IgG and IgA antibodies that neutralize SARS-CoV-2 entry by competition with ACE2 for binding the receptor-binding domain of the viral spike protein [88,89].

T helper cells (CD4) are responsible for cellular immunity and for helping B cells to produce neutralizing antibodies. Importantly, all B and T cells have immunological memory after a first contact with a pathogen. Memory CD4⁺ T cells mediate protective immunity against respiratory coronaviruses as well as neutralizing antibodies that bind the receptor binding domain in the spike of SARS-CoV were reported [90,91], suggesting that a similar immune response could be observed in individuals with COVID-19. The SARS-CoV-2 Spike glycoprotein is closely related to that of SARS-CoV 5 and some antibodies identified in SARS-CoV-infected patients could also neutralize SARS-CoV-2 [92]. But although cross-reactivity in antibodies binding to the Spike protein is relatively common, cross-neutralization responses between SARS-CoV and SARS-CoV-2 remain rare [93]. Convalescent sera from SARS-CoV and SARS-CoV-2 patients showed only limited cross-neutralization [94,95]. Pre-existing immunity could explain the relatively low confirmed cases in Africa. Pre-existing SARS-CoV-2-cross-reactive CD4⁺ and CD8⁺ T cells responses were observed in healthy people [96–98]. SARS-CoV-2 Spike glycoprotein-reactive CD4⁺ cells were found in 20%–60% of healthy individuals [96–98]. Very recently, the analysis of immune responses to SARS-CoV-2 from patients who recovered from COVID-19 identified targets of T-cell responses to SARS-CoV-2 and revealed cross-reaction with circulating ‘common cold’ betacoronaviruses due to past infections [97–102]. Children appear to be protected and develop mild COVID-19 or no disease [103–105]. Common human coronaviruses (HCoV-229E, HCoV-NL63, HCoV-OC43, HCoV-HKU1) were isolated from 7% to 11% in children hospitalized for acute respiratory tract infections [106–108]. Cross-reactivity between SARS-CoV-2 and human coronavirus is a plausible explanation for why children appear to be protected.

Another explanation is protection against SARS-CoV-2 induced by vaccines used against other pathogens. It seems that bacillus Calmette–Guérin (BCG) vaccination could protect from COVID-19. A strong association was observed between BCG vaccination deployment and COVID-19 mortality [109,110]. Countries where BCG vaccination is given at birth showed lower numbers of COVID-19 cases and deaths [111]. In fact, a SARS-CoV-2 envelope protein is closely related to a Mycobacterium bovis protein and BCG vaccine could induce a specific immunity against SARS-CoV-2 by targeting its essential viral envelope protein [112]. Moreover, the fatality rate due to COVID-19 was lower in Asian countries where Japanese encephalitis immunization is recommended compared with those were the population is not vaccinated [113].

Protection by repeated antimalarial treatments?

There seems to be an inverse relationship in the overall number of COVID-19 cases and malaria cases [110,114–116]. For instance, three of the African countries most affected by COVID-19 on 4 June 2020 are South Africa (37,525 cases and 792 deaths), Algeria (9733 cases and 673 deaths) and Egypt (28,615 cases and 1088 deaths), which belong to the countries less affected by malaria [117]. The use of antimalarial drugs to treat uncomplicated malaria in Africa could be another hypothesis explaining the relatively low number of confirmed cases in Africa [118]. Since 2002, the WHO has recommended the use of artesinin-based combination therapy (ACT) in the treatment of uncomplicated falciparum malaria (artemether-lumefantrine, artesunate-amodiaquine, dihydroartemisinin-piperaquine or artesunate-mefloquine) (Fig. 3). In 2018, these ACTs were widely used (Fig. 4). These ACTs, evaluated at plasma concentrations expected after oral uptake at the recommended doses used in uncomplicated malaria treatment, showed an in vitro inhibition of SARS-CoV-2 replication that ranged from 30% to 70% [119]. The combination mefloquine-artesunate was found to be the most effective in vitro against SARS-CoV-2. A patient treated with ACT for uncomplicated malaria could be protected from SARS-CoV-2 during treatment. Another study reported that some artemisinin derivatives used alone (dihydroartemisinin and artesunate) showed in vitro activity with median effective concentration (EC₅₀) around 10 μM [120]. Moreover, amodiaquine, a quinoline antimalarial and one of the partners of artemisinin derivative, was found to be active in vitro at a micromolar concentration against SARS-CoV-1 (2.5 μM) [121]. Another ACT partner, mefloquine, exerts in vitro cytotoxic effects onvero cells infected by SARS-CoV-2 at 10 μM [122]. A molecular docking study showed that pyronaridine, another ACT partner (artesunate-pyronaridine), can interact with the non-structural protein 5 (Nsp5), which is an essential protein for the transcription and replication of SARS-CoV-2 [123]. Pyrolaridine showed effective antiviral activity with EC₅₀ of 0.72 μM and pyronaridine is 165 times more concentrated in lungs than in plasma (Pradines B, unpublished data). The use of antimalarial
drugs and the dynamics of COVID-19 should now be compared on a country-by-country basis to confirm the potential effects of antimalarial drugs on COVID-19 transmission. It could be necessary now to evaluate clinically the efficacy of ACT to treat COVID-19, and more particularly that of mefloquine-artesunate, and the potential prevention of ACT against SARS-CoV-2 during malaria season, which currently begins in some African countries, taking into account the antimalarial drug, its dose, the number of treated patients, the number of cases of COVID-19 and deaths.

Conclusion

The comparison of European and African models of SARS-CoV-2 prevalence could provide important clues to the spread of the
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