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MALARIA ENDEMICITY OFFERS PROTECTION AGAINST CORONAVIRUS 2/COVID 19 PANDEMIC: WHY MOST AFRICAN COUNTRIES - NIGERIA MAY NOT RECORD MUCH FATALITY

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Abstract: The current article observed and analyzed malaria endemicity as a protective factor against the spread of coronavirus pandemic on African continent with special focus to Nigeria based on the fact sheet provided by World Health Organization (WHO) and Center for Disease Control (CDC) agencies across the world and Africa. From the analysis of the distribution of data, the endemicity of malaria offer protection to some population from COVID-19 outbreak in most African countries. This paper also provided important insight to the epidemiological pattern of COVID-19 pandemic in most African countries where malaria infection is endemic compared to Asia, Europe and America where malaria incidence are rarely found. Moreover, the molecular and genetic variations associated with malaria especially the Angiotensin converting enzyme II(ACE2) also play a protective role against coronavirus infection. Evidently the recovered patients in Nigeria and some other African Countries from coronavirus infection were mostly treated with anti-malaria drugs such as Chloroquine, Chloroquine derivatives, and *Artemisia anuua* derivatives drugs. This is a strong indication that the mechanism of action of these anti-malaria drugs performing the antiviral functions, suggest their similarity in molecular and genomic interaction why endemicity of malaria infection offers protection against coronavirus infection. Thispaper provides a better knowledge about the slowly spreading pattern of COVID – 19infections with insignificant fatality ratio in most African Countries especially Nigeria.

Keywords: Malaria, Protection, Coronavirus, Pandemic, Africa

Introduction

In recent times precisely between2000 and 2015, most malaria – endemic region in the world mark a tremendous decreasing malaria – related illnesses and deaths due to the innovations, scale-up of prevention and treatment therapies (Callahan, 2020).

However, the progress made in malaria prevention is being threatened by the rapid –spread of COVID – 19 pandemic.This disease does not respect boundaries or borders. The rapid spread of coronavirus disease (COVID-19) posed a great and unresolved threat to global public health with potential serious economic and social consequences. The World Health Organization and some scholars have expressed great concern about the global pandemic and, in particular, regarding the effect in the poorest African countries. The scarce economic resources, the weakness of the health system, and the endemic presence of diseases associated with compromised immunity make the containment of the outbreak a very difficult one. (Gilbert*et al.*, 2020).

Coronavirus emerged in Wuhan, China in November, 2019 and spread rapidly around the world. Itwas thought to have originated in bats and subsequently named Severe Acute Respiratory Syndrome (SARs)Coronavirus 2infections with this virus causing

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a pandemic in 2020 (Ashour*et al.*, 2020). Malaria is a widespread endemic disease that causes illness in approximately 230 million people and kills approximately 430,000 people each year. As at the end of April, 2020 there have been over 2,804,796 confirmed COVID-19 cases reported by the WHO with 193,710 deaths. Africa recorded 20,316 cases with about 839 deaths reported from 49 countries (WHO, 2020). In comparison, the WHO malaria report indicates that there was an estimated 228 million cases and 405, 000 deaths due to malaria globally in 2018, majority of which were from the African region. Given that complex arithmetic epidemiological pattern of COVID -19 pandemic and spread experiencing in Asia, Europe and African countries where malaria incidence wererarely seen. It is noteworthy to investigate and report the likely factors that may be responsible for this interesting phenomenon.

Materials and methods

Secondary data and historical research were applied.Various articles were reviewed starting from viral discoveries of coronavirus and malaria infection. Analysis of data provided by worldometer from December 2019 to June 2020, reports in periodicals and text were also reviewed to extract very important information.

Factual Issues about Coronavirus

Coronavirus is a group of related RNA virus that causes diseases in mammals and birds. The virus causes respiratory tract infection in human especially common cold which may vary from mild to severe infection.Other viruses such as rhinoviruses cause common cold in man. Severe or lethal varieties of illnesses are Severe Acute Respiratory syndrome (SARs), Middle East Respiratory syndrome (MERs) and Severe Acute Respiratory syndrome 2(SARs2)/ COVID -19.

Coronaviruses were first discovered in 1930s to cause an acute respiratory infection to domestic fowls known as infectious bronchitis virus (IBV) (ICTV, 2010).

Human coronavirus was discovered in 1960 with two novel strains B814 and 229E (Almeida, 2008). The novel strains B814, 229E, and IBV known as Organ culture OC43 had distinctive club-like spikes when observed with the election microscope (McIntosh*et al.*,1967). Thereafter other human coronaviruses have since been identified, that include SARs -CoVin 2003, HCoV NK63 in 2004, HCoV HKU in 2005, MERS-Cov in 2012 and SAR- CoV-2 (COVID-19) in 2019 (Zhu, 2020). Bats and birds, warm –blooded flying vertebrates are an ideal natural reservoir for the coronavirus Bats are the reservoirs for alpha-coronaviruses and beta-coronavirus while birds are the reservoir for gamma-coronaviruses and delta-coronaviruses (Forni*et al.*,2017). Six species of human coronaviruses are known, with one subdivided into two different strains, making seven strains of human coronaviruses.

Altogether four human coronaviruses known to produce mild symptoms are:

Human Coronavirus OC43 (HCoV – OC43) β-CoV.; Human Coronavirus HKUI (HCov –HKUI), β-CoV.; Human Coronavirus 229E (HCoV – 229E), α-CoV.;Human Coronavirus NL63 (HCoV-NL63), α-CoV.

Three coronaviruses known to produce severe/ lethal symptom include:

Middle East respiratory syndrome-related coronavirus (MERsCoV), β-CoV.; Severe acute respiratory syndrome coronavirus (SARs-CoV) βcoV. ; Severe acute respiratory syndrome coronavirus 2 (SARs-CoV-2), β-CoV/ COVID-19.

The human coronaviruses HCoV- OC43, HCov –HKUI, HCoV – 229E, and HCoV- NL63 continually circulate in the human population and produce the mild symptom common cold in adults and children worldwide, and these coronaviruses cause about 15% of common colds, while 40 -50% of colds are caused by rhinoviruses (Corman, *et al.*, 2018). Coronaviruses are large, roughly spherical, particles with bulbous surface projection, measuring average diameter 125nm

(125µm) diameter of envelope 85 nm and the spikes 20nm long as shown by electrons micrograph (Fehr & Perlman, 2015). The viral envelope consists of a lipid bilayer, in which the membrane (M), envelope (E) and Spike(S) structural protein are anchored, the ratio of E:S:M in the lipid bilayer is approximately 1:20:300, each coronavirus has 14 surface spikes (Neuman*et al.*,2011). Infection begins when the viral protein attaches to its complementary host cell receptor. After attachment, a protease of the host cell cleaves and activates the receptor-attached spike protein, depending on the host cell protease available, cleavage and activation allows the virus to enter the host cell by endocytosis or direct fusions of the viral envelope with the host membrane. Inside the host cell the virus particle is located and its genome enters the cell cytoplasm (Fehr &Perlman, 2015). Common symptoms of COVID – 19 include: fever, cough, fatigue, shortness of breath, loss of smell and tested, sore throat which in majority of cases result in mild symptoms some progress to severe acute respiratory distress syndrome usually precipitated by a cytokine storm, multi-organ failure, septic shock, and blood clots. The incubation period of coronvirus infections ranges between 5 – 14 days (WHO, 2020).

COVID – 19 or SARs – COV – 2 is closely related to the original SARs –CoV which is thought to have animal zoonotic origin, all features of the novel SARs – COV – 2 viruses occur in related coronaviruses in nature (Andersen et al, 2020). The lungs are the organs most affected by COVID- 19 because the virus accesses lost cells via the enzyme angiotensin converting enzyme 2 (ACE2) which is most abundant in type II alveolar cells of the lungs, coronavirus uses a special surface glycoprotein the spike (Peplomer) to connect to ACE2 and enter the host cell (Verdecchia*et al.*,2020). The density of ACE2 in each tissue correlates with the severity of the disease in that tissue and some scholars have suggested decreasing ACE2 activity might be protective, though another view is that increasing ACE2 using angiotensin II receptor blocker medications could be protective (Zhang *et al.*, 2020).

Coronavirus invades the central nervous system (CNS) gastrointestinal organs as ACE2 is abundantly expressed in the glandular cells of gastric duodenal and rectal epithelium as well as endothelial cells and enterocytes of the small intestine (Humming *et al.*,2020).

The severity of COVID -19 varies from a mild course with few or no symptoms with recovery within 2 weeks to severe or critical disease which may take up to3 weeks to six weeks to recover (WHO, 2020). Children are less susceptible with about 1% of cases being under 10 years and 4% for age 10 – 19 years. These ages usually have milder symptoms and lower chances of severe disease than adult, in those younger than 50 years the risk of death is less than 0.5%, while in the elderly 70years and above it is more than 8% (Dong *et al.*,2020). Pregnant women may be at higher risk for severe infection with COVID-19 on data from other similar virus, like SARs and MERs, though the data for COVID-19 is not yet available (Fang *et al.*,2020). Majority of the patient who died of COVID-19 have pre-existing underlying health conditions such as hypertension, diabetes mellitus and cardiovascular disease (Qin *et al.*, 2020).Patients with depressed immunity are equally susceptible to COVID-19.

It is unclear yet if past infection provides effective or long-term immunity in people who recover from the disease (Schrger, 2020). Although some other study observed that some infected persons develop protective antibodies so acquired immunities presumed likely, based on the behavior of other coronaviruses cases in which recovery from COVID-19 was followed by positive tests for coronavirus at a later date have also been reported (Omer *et al.*, 2020). However, these cases are believed to be lingering infection rather than infection or false positives due to remaining RNA fragments (Parry, 2020). A study carried byKorean CDC on 285 individuals who tested positive for SARS-Cov-2 in PCR tests administered days or weeks after recovery from COVID-19 found no evidence that these individuals were contagious at this later time (KCDC, 2020). Other studies observed that some other coronaviruses circulating in people are capable of re-infection after roughly a year (CUCN, 2020).

In the U.S. a greater proportion of deaths due to COVID-19 have occurred among African Americans, due to structural factors that prevent African American from practicing social distancing, concentration in crowded substandard housing and in essential occupations such as public transits, and health care (Dorin, 2020). Higher prevalence of lacking health insurance and case of underlying health conditions such as diabetes, hypertension and heart diseases also increases their risk of death (Adams, *et al.*,2020).

Human coronaviruses infect the epithelial cells of the respiratory tract, while animal coronaviruses generally infect the epithelial cells of the digestive tract, SARs coronaviruses, for example, infect via an aerosol route, of the human epithelial cells of the lungs by binding to the angiotensin converting enzymes 2 (ACE 2) receptor (Decaro *et al.,* 2011).

Malaria is a mosquito-borne infectious disease caused by single –celledmicroorganisms – Plasmodium (Phylum Apicomplexa) (WHO, 2014). In humans, malaria is caused by *P. falciparum, P. vivax, P. malariae, P.ovale,* and *P. knowlesi*(Colli, 2012).

Malaria signs and symptoms typically begin 8 – 25 days after female infected, *Anophelis* mosquito bite a healthy individual (Nadjm& Electrons, 2012). Initial manifestations of the disease common to all malaria species are similar to flu-like symptoms, and can resemble other conditions such as sepsis, gastroenteritis, and viral diseases, the presentation may include headache, fever, shivering, joint pain, vomiting, hemolytic anemia, jaundice, hemoglobin in urine, retinal damage and convulsions (Bartoloni & Zammarchi, 2012).

Scientific Assumptions

The assumption that malaria offers a protective effect against the recent SARs Cov-2 / COVID -19 infection in malaria endemic area especially in Africa are based on the following verifiable facts below:

The presence of an evolutionary adaptation related to malaria (in the endemic areas or in those areas where malaria has been eradicated) might play a role in limiting the spread of COVID-19 (Napoli &Nioi, 2020). Some variants of the ACE 2 receptor used by the coronavirus to infect cells, may protect those endemic populations (Driss *et al.,* 2020). A multi-center study, based on genetic epidemiology, proposed an association between the occurrence of single nucleotide polymorphisms in the gene encoding the C1 alpha – S sub unit and individual susceptibility to severe, malaria demonstrating that G-protein coupled receptor (GPCR) signaling in host has an influence at the disease level (Auburun*et al.*,2008, 2010). The renin-angiotensin system (RAS) a protolyticcascade that generates peptides that binds and signals through GPCRS. In this peptidergic system, angiotensin II (Ang2) is formed from the enzymic cleavage of angiotensinogen to angiotensin I(Ang 1) by aspartyl protease renin, with subsequent conversion to Ang II by angiotensin converting enzyme (ACE) (Mizuiri and Ohashi, 2015). AngII exerts its actions via AT1 and AT2 receptors, which in principle, mediate opposite functions. AT1 receptors promote vasoconstriction, thirst and release of vasopresin and aldosterone, fibrosis, cellular growth, and migration (Fyhrguist and Saijonmga, 2008). Angiotensin II receptor on the other stimulation leads to vasodilatation, release of nitric Oxide (NO) natriuresis, and inhibition of growth. However the activity of both receptors maybe altered by oliogomerization association with various interacting proteins or ligand independent effects (Villola*et al.*, 2015). Angiotensin (1-7) has its actions mediated specific by the mitochondrial assembly (MAS) receptor which include vasodilation by amplifying the effects of bradykinin, stimulating cyclic guanosine monophosphate (cGMP) synthesis and inhibiting the release of nor epinephrine (Ferrario, 2006). The expression and activity of ACE2 is up-regulated by treatment with ACE inhibitors, such as captopril, promoting increased local production of Ang (1-7) (Ferraio *et al.,* 2005). Some studies reported an apparent protective effect of AngII in malaria. A genetic association study was carried out in Orissa India, to search for a possible influence of polymorphisms in angiotensin 1 – converting enzyme (ACE) and angiotensin II – converting enzyme (ACE2) on the outcome of malaria. The study observed that allele of ACE1/D polymorphism, which increases Ang2production is associated with mild malaria. ACE2 C – T substitution, a polymorphism that reduces ACE2 expression in the presence of the T allele also results in an increase in Ang2, by reducing its conversion to Ang (1- 7) (Dhangadamachi*et al.,* 2020). Further evidence that ACE and ACE2 polymorphism and consequent increased plasma levels of Ang2 are associated with malaria severity was demonstrated in people with an African genetic background (Gallego-Delgado and Rodriguez, 2014). In African population, it seems that these polymorphisms confer protection from severe malaria in childhood but deleterious effects, such as hypertension in adulthood (Gallego-Delgadoand Rodriguez, 2014). Studies have it that angiotensin peptides inhibit the sexual and blood stage of avian as well as human parasites. Malaria presents a multi-symptoms disease and as well increases in parasitemia, other parasite-host-interactions are important in the pathogenesis of the disease. The syndrome is marked by intense inflammatory immune responses, sequestration of leukocytes and parasitized erythrocytes in the microvasculure. Involvement of angiotensin peptides in the regulation of immune system has been suggested (SilvaFilho*et al.,* 2015). Angiotensin converting enzyme 2 (ACE2) is an enzyme attached to the outer surface cell membranes of cells in the lungs, arteries, heart, kidney, and intestine (NBCI, 2020).

ACE2 lower blood pressure by catalyzing the hydrolysis of angiotensin II (avasoconstrictor peptide) into angiotensin (1-7) avasodilator (Wang *et al.,* 2016). ACE2 serves as the entry point into cell for coronaviruses that cause severe acute respiratory syndrome coronavirus 2 / COVID -19 (NBCI, 2020). The human version of the enzyme is often referred to as hACE2 (Kasmi*et al.,* 2019). Angiotensin converting enzyme endothelia and other cells (Turner, 2015). The expression of ACE2 in cortical neurons and glial cells make susceptible to a SARs-CoV 2 attack which was the basis of anoxia and incidences of neurological defaults seen in COVID-19 (Baig, 2020). As a trans-membrane protein ACE2 serve as the main entry point into cells for some coronaviruses which include HCoV-NL63; SARs-CoV (the virus that cause SARs) and SARs-CoV2 (The virus that causes COVID-19) (Lewis, 2020). The binding of the spike S1 protein of SARs – CoV and SARs-CoV2 to the enzymatic domain of ACE2 on the surface of cells results in endocytosis and translocation of both the virus and the enzyme into endosomes located within cells (Millet and Whitetaker, 2018). The entry process requires priming of the S protein by the host serine protease TMPRSS2, the inhibition of which is under current investigation as a potential therapeutic (Akbarshakh and Eldurado, 2020). Both ACE inhibitors and angiotensin II receptor blocker (ARBs) that are used to treat high blood pressure have been shown in rodents studies to up regulate ACE2 expression hence may affect the severity of Coronavirus infections (Diaz, 2020). The second point was based on the treatment used for malaria infection which is widely used in the treatment of COVID-19. These drugs include Chloroquine, and its derivatives hydroxychloroquine, and *Artemsiaanuua*extract. These drugs have shown to be very effective in treating COVID-19. Recently, some authors have reported the usefulness of hydroxychloroquine at a dosage of 400mg per day for ten days in the treatment of symptomatic SARs-CoV 2 Pneumonia (Dyall*et al.,* 2017). Again Chloroquine is commonly used in several countries in the treatment and prevention of malaria despite drug resistance or government recommendations in Sub-sharana Africa due to its availability less expensive (Ocan*et al.,* 2019). Other drugs similar to Chloroquine such as amodiaquine, and mefloquine sometimes used in combination with artemisinin are also widely used in Africa as anti malarias with antiviral action against SARs-COV and MERs-CoV and also even some medications used in cases of Chloroquine resistance (e.g. doxycycline, azithromycin) have demonstrated antiviral action against a large group of virus (D'Alessandro *et al.,* 2020). The analysis of epidemiological data on malaria and the effectiveness of antimalarials in the treatment of Beta-CoVs diseases, it is possible to state that scientific research is expected to verify the potentials of antimalarials in reducing the spread of COVID-19 even in non-African countries. Again, the effect of the administration of Chloroquine derivatives in areas where malaria is endemic seems to preserve these geographic area especially the least developed counties in Africa from COVID-19 outbreak, despite some rare side effects (Napoli and Nioi, 2020).

Analysis and Result

Table 1: **The Global Death-to-Case Ratio of COVID – 19 According to 6 Regions of the World**

Six Region of The World	Total confirmed Case (TCC)	Total Death (TD)	Total Recovery (TR)	Total Active Case (TAC)	Total critical situation (TCS)	TDCR = TD /TCC for each region (%)
Africa	385,219	9,692	185,243	190,278	907	2.51%
Asia	2,211487	54,786	1,440,639	716,062	19,372	2.50%
Europe	2,413,519	190,725	1,350,296	872,498	5,773	7.90%
North America	3,081,414	166,962	1,334,920	1,574,231	18,833	5.42%
Oceanic	9,326	126	8,570	630	1	1.35%
South America	2,146,835	82,342	1,232,788	831,705	12,780	3.84%

World Death –to-Case ratio = 504366/ 10,242,932 = 4.9%.

Discussion

The hypothesis:Malaria endemicity offers protection against coronavirus diseases 2019 (COVID -19) disease. In Nigeria, malaria infection shares most common symptoms with COVID-19 disease such as fever, flu, cough, scratching of throat, headache, body aches and weakness. Malaria can coexist with many other infections. Consequently, confirming malaria infection with diagnostic test does not rule out the possibility that such patient might also test positive for coronavirus or COVID-19 (WHO, 2020). Again even before the pandemic in 2019 these symptoms of flu, cough, shortness of breath and fever are usually treated with the anti-malarial drugs in Nigeria.

At the advent of COVID-19 Pandemic, scholars and the world Health organization (WHO) have expressed great concerns about the global pandemic regarding the involvement of the poor African counties due to scarce economic resources, the weakness of the health system, and the presence of endemic diseases associated with immunodeficiency i.e. HIV/AIDS may make the containment of the outbreak particularly difficult (Gilbert*et al.,* 2020). Interestingly considering the epidemiology of COVID -19 in some African Countries where malaria infection is endemic clearly showed that most of their predictions were untrue about the African continent (Worldometer, 2020).

The death-to-case ration (**TDCR)** reflects the number of deaths divided by the number of diagnoses cases within a given time interval.

Based on Johns Hopkins university statistics, the global death-in-case ratio is 6.4% Translate to: Total number of death due to COVID-19 divided by Total number of confirmed positive cases multiply by 100% (345,375/5, 428, 605)as at 25th May, 2020.

The ratio varies by region (JHU, 2020; Lassarini and Putoto, 2020). The African death-to-case ratio was small compared to other continent of the world.

Other epidemiology measures include the case fatality rate (CFR), which reflects the percentage of diagnosed individuals who die from a disease and the infection fatality rate (IFR), which reflects the percentage of infected individuals (diagnosed and undiagnosed) who die from the disease. These statistics are not time-bound and follow a specific population from infection through case resolution. Many academics have attempted to calculate these numbers for specific population (Our world in data, 2020).

In Nigeria going by the figures authenticated by NCDC (CFR) and (IFR) are quite low and insignificant considering the number of over six month about 200,000,000 populations have been exposed considering the inadequate adherence to COVID-19 prevention of spread protocol suggesting that coronavirus may have been a co-infection with malaria over ages in these part of the Africa (NCDC,2020).

Again an inquest into the likelihood of a malaria patient testing positive for COVID-19 is needed in malaria endemic region of Africa.

The table below clearly shows the Death –to-Case ratio which mortality each region of the world have surfaced as of June 27th, 2020. The analysis Oceania region had the least Death –to-Case ratio of 1.36 followed by Asia with 2.50% followed by North America 5.41% and South America 3.84%. The world case fatality of COVID-19 from December, 2019 to 27th June, is 4.9%. The raw data above was extracted from worldometers.info/coronavirus before the analysis.

From the table below Oceania, Asia and Africa had lower Death-to-Case ratio. Some counties in Oceania region such as Australia, and Paupa New Guinea have malaria infection likewise some countries in Asia regions like, India,

Malaysia and Indonesia also have malaria infection.

In Africa region malaria infection is highly endemic in both dry and wet seasons. Oceania region account for lowest confirmed case may be due to population, location as well as less frequent interaction with the rest region of the world.

Although COVID-19 pandemic began in Asia in Wuhan, Hubei, China and spread widely through the continent the lower Death-to-Case ratio may be as a result of inappropriate report of the death resulting from COVID-19 (Tom Allavd, 2020).

Interestingly, considering the reported Death-to-Case ratio of COVID-19 in African Continent for the past 6 months despite the lack of standard health facility and malaria endemicity which is not at check since COVID-19 began in December, other hypothesis that malaria infection offers protection to COVID -19 pandemic may be considered fact.

Other research that maybe very necessary to be considered is whether a patient/person that is down with malaria infection will not test positive for COVID-19/ coronavirus severe acute respiratory syndrome 2.

It is also important to note that as soon as the anti malaria drug are administering to a patient that is down with malaria infection the fever and the flu symptom will cease.

Exposure to viral infection to asusceptible host does not take longer period before the establishment of the disease. The 6 months of constant exposure of Nigerians and majority of African countries to the viruses responsible for the pandemic considering the difficulties toward the adherence to preventive measures; suppose to have made African continent an epicenter than all other regions of the world.

Conclusion

In conclusion, the review highlights important points related to some misconception and confusion and present by some article that Africa may soon be an epicenter for coronavirus Severe Acute Respiratory syndrome 2 / COVID – 19 considering Death-to-Case ratio for the past 6 months. Most African Countries are endemic to malaria infections which assume to offer protection against novel coronavirus that causes Severe Acute Respiratory syndrome 2 responsible for COVID - 19 pandemic.

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