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COVID-19 and malaria in sub-Saharan Africa: Holistic diagnostic approaches may promote effective clinical case management

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ABSTRACT

Since the start of 2020 the rapidly escalating number of deaths from confirmed cases of Coronavirus disease (COVID)-19 has become a major global public health concern. With the existing significant burden that malaria poses in sub-Saharan Africa, it is clear that in this low-income region the cumulative effects of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and Plasmodium infections will devastate already fragile national economies. In turn, this will have a severely deleterious impact on under-resourced, overstretched and overwhelmed health care systems. The similarities in the clinical signs and symptoms of these two febrile diseases and the availability of very few COVID-19 molecular diagnostic centres might contribute significantly to the difficulties experienced in the sustainable management of these twin public health threats. Here, decentralization of validated rapid diagnostic kits for parallel testing of suspected cases of COVID-19 and malaria in health care centres is described. We argue that for both urban populations and underserved rural communities in sub-Saharan Africa the use of malaria and COVID-19 rapid tests as a dual holistic diagnostic approach in patient care settings may promote more effective control and facilitate appropriate treatment of each disease.

Introduction

The emergence in Wuhan, China, in late 2019 of clinical cases of what was subsequently designated as novel Coronavirus disease (COVID)-19 has been assigned a serious Public Health Emergency of International Concern [1]. This illness, caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), is a highly pathogenic and transmittable viral infection [2]. Primarily through international travel-associated spread of infection, the COVID-19 pandemic has since reached 188 countries or territories, with more than 14.8 million confirmed cases of infection and over 613,000 deaths as of 21st July 2020 [3]. Moreover, the Africa Centres for Diseases Control and Prevention have reported 721,563 cases and 15,169 deaths to date [4]. These relatively low figures from Africa are attributed to inadequate diagnostic capacity leading to disproportionately fewer tests performed, rather than to a paucity of virus in circulation or a lesser proportion of positive tests than has been reported from other regions of the world [5,6].

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Malaria is a potentially deadly vector-borne protozoan parasitic disease that is an enduring global public health problem. Infection of humans is caused by each of five *Plasmodium* spp. (*P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae* and *P. knowlesi*) that are transmitted via the bite of blood-feeding, infectious female *Anopheles* mosquitoes [7].

From the statistics for global malaria incidence released most recently by the World Health Organization (WHO), of 228 million cases of infection and 405,000 deaths reported in 2018, African countries contributed 93% infection and 94% deaths, respectively [8]. Comparing this with data for 2017, when 219 million infections were recorded, there was a 9 million increase in confirmed clinical cases of malaria despite the considerable control and preventive measures [9].

In the face of concerted ongoing efforts around the world to defeat the COVID-19 pandemic several warnings have been issued to countries in sub-Saharan Africa not to lose focus on other infectious diseases of public health concern, of which malaria is of paramount importance [10, 11]. Furthermore, it was predicted that any neglect in sustaining effective management of malaria control and treatment strategies might result in the death of 769,000 people in sub-Saharan Africa in 2020 alone [12]. This would represent a level of malaria mortality not seen for two decades. Such inattention may arise through the diversion, intentional or inadvertent, of previously allocated national public health resources to addressing the immediate infection diagnosis, therapy and control demands resulting from the emergent COVID-19 crisis.

In a bid to prevent realization of this unfortunate prediction and in order not to allow COVID-19 control strategies to jeopardize existing efforts to reduce global malaria morbidity and mortality rates by at least 90% in 2030, the WHO Global Malaria Programme is leading a collaborative effort involving its regional and national offices in malaria-endemic countries [12]. The aim is to mitigate as much as possible the negative impact of SARS-CoV-2 on malaria incidence, detection and treatment, while concurrently contributing to a successful COVID-19 response. Some of the identified approaches are the sustainability of malaria prevention and control, the widespread implementation of effective testing and prompt medical treatment [13,14].

In this article, we emphasize the need to validate rapid diagnostic kits specific for COVID-19 infection and, as a matter of urgency, to decentralize their distribution, together with that of similar kits to diagnose malaria, to all health care centres in malaria-endemic countries. This is considered necessary as the two febrile infections share several overlapping clinical signs and symptoms. Hence, a parallel and more cost-effective confirmatory (diagnostic) approach should not only distinguish between these diseases of major global health concern, but also facilitate rapid and effective medical responses [10,11].

Clinical manifestations of COVID-19 and malaria infections

COVID-19 is a respiratory tract infection that is caused by SARS-COV-2, a new member of the coronavirus group of enveloped, positive-sense, single-stranded RNA viruses which cause disease in mammals and birds. Typically, transmission occurs via virus-laden droplets propelled from mucus and saliva when an infected individual sneeze, coughs or talks. These large droplets penetrate the mucous membranes when they alight on, or are inadvertently transferred to, the mouth nose or conjunctiva of another person in close proximity. Transmission may also be indirect, by touching an inert surface on which droplets have recently landed. Aerosols, droplets sufficiently small to be suspended in the air, may provide a minor mode of transmission over further distances [15]. The common clinical features of mild infection with SARS-CoV-2 include fever, cough, sore throat, headache, fatigue, myalgia and breathlessness. In complicated cases, which may be severe and often fatal, symptoms such as hypoxaemia, acute respiratory disease syndrome, arrythmia, shock, acute cardiac injury and acute kidney injury persist [16,17].

In contrast, malaria is caused by obligate protozoan parasites of the genus *Plasmodium* that have a lifecycle which involves a broad array of vertebrate hosts fed upon by haematophagic insects [7]. However, despite very different causative agents in human's malaria shows some clinical features strikingly similar to those of COVID-19. Common clinical signs of uncomplicated malaria include fever, rigors, myalgia, chills, sweats, headache, vomiting, watery diarrhoea and mild anaemia. Complications from infection are usually characterized by severe anaemia and at least one of the following multi-organ dysfunctions: central

nervous system (cerebral malaria); pulmonary system (respiratory failure); and renal system (acute renal failure) [18,19].

It should be noted that both COVID-19 and malaria can be asymptomatic in some infected individuals, who are nevertheless potentially infectious. For COVID-19 it appears that this can occur upon first exposure while for malaria it follows prolonged exposure in endemic settings. Such undetected reservoirs of infection affect population level infection dynamics by raising the likelihood of community transmission through their respective appropriate channels [20].

Laboratory testing for COVID-19 and malaria

A suspected case of COVID-19 infection is first subjected to a symptoms-based diagnosis and the patient's possible contact history with infected persons is also considered [5,21]. As the spread of SARS-CoV-2 continues to escalate across all the regions of Africa, the reliance on this predictive diagnosis strategy becomes increasingly questionable. This is due to a high level of similarity in the clinical signs and symptoms between COVID-19 and malaria [20]. Therefore, in order to exert an element of control over the dissemination of SARS-CoV-2 and to achieve an appropriately tailored medical response to these two life-threatening diseases, it is strongly advisable to validate an initial symptoms-based observational diagnosis with confirmatory diagnostic tests [21].

At present, molecular diagnosis using the real-time reverse transcription-polymerase chain reaction (RT-PCR) assay is acknowledged to be the 'gold standard' for SARS-CoV-2 testing [22]. This is because it is a highly sensitive and specific laboratory diagnosis for COVID-19 case identification, which may be used to inform contact tracing and to rationalize infection control measures [23,24]. Following the high-throughput sequencing of the complete genome of spatio-temporally distinct SARS-CoV-2 isolates (ranging in size from 29.8 to 29.9 kb) and their deposition in publicly accessible databases [25,26], a number of diagnostic kits and primers for molecular identification have been produced by pharmaceutical companies and research teams. Samples for SARS-CoV-2-specific RT-PCR are usually collected from the upper respiratory tract (nasopharyngeal and oropharyngeal swabs) but also from a fresh stool specimen and, in severe cases, an aliquot of peripheral blood [16,17]. The viral genomic RNA extracted from each sample is converted to DNA using RNA-dependent DNA polymerase, a process that is followed by amplification of the specific DNA fragment [27].

In malaria-endemic regions, light microscopical examination of a Giemsa-stained blood film to detect intraerythrocytic parasites is the established confirmatory test of choice [28]. This remains the benchmark diagnostic tool over other approaches, including laboratory-based molecular tests such as RT-PCR using parasite DNA-specific primers. When performed by a trained technician it provides both qualitative and quantitative information in terms of infecting *Plasmodium* spp. In addition to its proven sensitivity and reliability, sample preparation is easier when compared to the procedure for nucleic acid-based diagnosis, it can be undertaken in the field using rudimentary facilities and easily transported consumables [29,30].

Despite the high level of sensitivity and specificity of RT-PCR and other molecular-based diagnostic approaches for COVID-19 and malaria, these sophisticated testing strategies require expensive equipment and consumables, highly trained expertise and are time-consuming to perform [30,31]. As a result, they are available only in accredited reference laboratories and a very few health care centres throughout sub-Saharan Africa.

Rapid diagnostic tests

Rapid diagnostic tests (RDTs) are point-of-care immunochromatographic tests that are tailored towards the specific detection of antigens or antibodies peculiar to a particular infectious disease. In malaria-endemic regions, the use of RDTs has gained significant momentum, especially in primary health care centres, for the detection of *Plasmodium*-specific antigens in blood samples [30]. This is due to the fact that most of the commercially available malaria RDTs satisfy the guidelines for the WHO's ASSURED (Affordable, Sensitive, Specific, User-friendly, Rapid and Robust, Equipment-free, and Deliverable to end-users) criteria for appropriate diagnostic assays [32,33].

With the increasing incidence of COVID-19, scarcity of molecular diagnostic reagents and overwhelming demand placed on the small number of existing molecular diagnostic centres [31], extensive efforts are currently devoted to developing RDTs that can specifically target

actively dividing SARS-CoV-2 nucleocapsid protein from respiratory samples (e.g. sputum specimen, throat or nasal swab). An advantage of this test is its ability to identify early and acute infection. Other rapid tests are tailored towards detecting anti-SARS-CoV-2 antibodies (IgM and/or IgG) in the blood sample of infected patients. Serological testing is essential for the detection of current or prior infection with SARS-CoV-2, from which a person's potential immunity to reinfection may be assessed. However, antibodies are generally produced days to weeks after exposure to a disease-causing agent. As a result, unlike antigen testing kits serology lacks the capacity to detect early infection. In addition, the production of antibodies may be compromised in elderly people and those individuals having certain underlying diseases such as diabetes and HIV/AIDS [34,35]. Each of these factors might adversely affect the efficiency of antibody testing.

Appropriately validated RDTs designed specifically for the detection of SARS-CoV-2 antigens offer advantages over alternative diagnostic strategies by enabling a faster, cheaper, easier and earlier confirmation of infection in both symptomatic and asymptomatic patients.

Discussion

Considerable efforts have been channeled towards sustainable management of malaria infection in sub-Saharan Africa, where, despite significant progress in recent times to reduce the burden of disease, unacceptably high infection and fatality rates are still recorded each year [8,36,37]. In fact, it was predicted that by 2030 not only would 35 endemic countries be malaria-free but also a reduction of at least 90% in global malaria incidence and mortality should be achieved [12]. With the additional heavy burden of the COVID-19 pandemic that the world is now experiencing it can be reasonably assumed that the poor health care infrastructure and fragile economy in sub-Sahara African countries will be overstretched beyond their elastic limit [38]. In response to the heightened public health response to the worldwide spread of SARS-CoV-2, the WHO has urged malaria-endemic regions not to relent on their commitment to established strategies for malaria prevention, diagnosis and treatment. It recommended that anyone in those localities experiencing symptoms of fever should immediately seek diagnosis and medical attention [13].

In combatting any infectious disease outbreak, active surveillance and early detection are crucial to the strategic management and effective implementation of control measures [39,40]. However, in the particular scenario of COVID-19 and malaria in sub-Saharan Africa the close resemblance of their clinical signs and symptoms combined with the low capacity for sensitive, molecular detection of SARS-CoV-2 is likely to result in series of incorrect diagnoses, thereby leading to inappropriate treatment and, ultimately, uncontrolled spread of COVID-19 [5,6,20].

In a bid to address this serious public health challenge to sub-Saharan Africa, RDTs that detect SARS-CoV-2 antigens must be validated as a priority. Moreover, together with *Plasmodium*-specific RDTs, approved diagnostic tests for COVID-19 should be decentralized immediately to health care centres in urban and underserved regional communities alike. This holistic parallel diagnostic approach will differentiate between COVID-19 and malaria with greater accuracy than do tests currently available and thus enhance the effectiveness of patient treatment and infection control measures. Interestingly, the proposed testing strategy is cheaper, faster and easier to operate compared to molecular and microscopy-based means of diagnosis [30].

Conclusion

The ongoing community transmission of SARS-CoV-2 infection across sub-Sahara Africa may negatively impact established guidelines for control of malaria in the region of the world most affected by this major public health burden. Taking into consideration factors such as a high level of similarity in the signs and symptoms of COVID-19 and malaria, inadequate provision for the molecular diagnosis of SARS-CoV-2, and the ill-equipped health care infrastructure in almost all African countries, it may be reasonably assumed that the parallel management of these two deadly infectious diseases will be difficult to achieve.

In recognizing in mid-2020 this issue of growing regional health concern, we advocate for the urgent validation and decentralization of cost-effective and easy-to-use RDTs for the testing in tandem for COVID-19 and malaria in primary, secondary and tertiary health care centres throughout sub-Saharan Africa. It is envisaged that adopting this holistic approach will enhance diagnostic accuracy and thereby increase rates of appropriate treatment for both COVID-19 and

malaria. In turn, this will further the sustainable clinical case management of each of these life-threatening diseases, which will help to alleviate their considerable public health burden to afflicted communities.

Authors contribution

All authors contributed substantially to the development and the writing of this article as indicated. Conception, ROM and AWT-R; article collation and analysis, ROM and DI; writing-original draft preparation, ROM and DI; writing-review and editing critically for important intellectual content, AWT-R. All authors read and approved the final version of the manuscript.

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