



Perspective

COVID-19 and syndemic challenges in ‘Battling the Big Three’:
HIV, TB and malaria★

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ABSTRACT

Indirect effects of the COVID-19 pandemic have the potential to seriously undermine the health system in sub-Saharan Africa with an increase in the incidences of malaria, tuberculosis (TB) and HIV infections. Based on current evidence in the African region the collateral impact of COVID-19 on the “big three diseases” shall be addressed in the following.

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Malaria and COVID-19

All countries where malaria is endemic have reported COVID-19 cases. The WHO African Region has experienced >1.5 million cases of COVID-19 (WHO, 2020a) and bears 90% of the global malaria burden. Significant efforts have led to a substantial reduction in malaria deaths in the last decade (WHO, 2019a) and enduring sustainability of malaria interventions and control programs is essential. As signs and symptoms of COVID-19 and malaria partly overlap, diagnostic guidance is inevitable in malaria-endemic settings. Also, young adults can be asymptomatic for long periods of time when infected by either malaria or COVID-19. There is a need for increased awareness of COVID-19/malaria co-infection

and further guidance for clinicians on the importance of testing for other causes of disease (Chanda-Kapata et al., 2020).

The WHO World malaria report 2020 acknowledges the major disruption in essential malaria services (WHO, 2020b). In sub-Saharan Africa, a region with more than 90% of all malaria infections, the spread of COVID-19 was slower with lower mortality rates. Possible causes include a rather young population and a relatively high rural population with limited mobility (Massinga Loembe et al., 2020). The Malaria Atlas Project conducted modeling to quantify the potential impact of service interruptions due to the COVID-19 pandemic. The analysis showed that when all campaigns are suspended and a 75% reduction of access to effective antimalarial drugs applies, 769,000 people could die from malaria in sub-Saharan Africa by the end of 2020 (WHO, 2020c). Also, 31 countries (34%) are estimated to have increased incidences, with 15 countries (16%) estimated to have an increase of 40% or more in malaria case incidences in 2020 compared to 2015 (WHO, 2020b). The projections presented in the WHO report indicate that despite worthy global and national efforts to maintain essential malaria services, malaria morbidity and mortality are likely to be higher than expected in 2020 (WHO, 2020b).

Cameroon reported a significant increase in malaria cases and deaths during the COVID-19 pandemic (Kindezka, 2020). In April 2020, Zimbabwe reported a surge in malaria outbreaks (Cassim,

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2020) and deaths were attributed to the shortage of antimalarial drugs and lack of access to healthcare (Nghochuzie et al., 2020). By using a geospatial model, it was concluded that COVID-19-related interference will cause a significant increase in malaria cases and even doubling malaria mortality in 2020, with still greater increases in subsequent years (Weiss et al., 2021). Another study on the interruption of prevention activities by using malaria transmission models predicted also that the malaria burden could have doubled in 2020, compared to 2019 (Sherrard-Smith et al., 2020). Estimates indicate that reducing case management for six months and delaying the distribution of long-lasting insecticidal bed-net campaigns in Nigeria could lead to 81,000 additional fatalities; corresponding figures apply to other countries (Sherrard-Smith et al., 2020).

SARS-CoV-2 infects lung alveolar cells using receptor-mediated endocytosis via the angiotensin-converting enzyme II (ACE2) as entry receptor (Zhou et al., 2020), and SARS-CoV-2 infection depends on the receptors ACE2, TMPRSS2, and CD147 (Sienko et al., 2020). A genetic deletion/insertion of a 285 bp Alu repeat sequence in intron 16 of the *ACE* gene fragment insertion (I allele) or its absence (D allele) is of particular importance. Insertion of the extra fragment (ACE I allele) is associated with lower ACE activity, whereas its absence (ACE D allele) leads to higher ACE activity (Woods et al., 2000; Manning and Fink, 2020) and angiotensin II levels (Sarangerajan et al., 2020). While the ACE I/D genotype modulates ACE2 expression and the ACE D allele is associated with the infection course and mortality due to COVID-19 (Delanghe et al., 2020; Yamamoto et al., 2020), an earlier study has shown that the ACE I/D and ACE D/D genotypes provide relative protection from cerebral malaria in an Indian cohort (Dhangadamajhi et al., 2010). The protective association of the D allele is conclusive, as angiotensin II and its analogues have antimalarial effects in *Plasmodium falciparum* infection (Torres et al., 2016; Maciel et al., 2008). The ACE I/D allele distribution (rs4646994, ACE I/D polymorphism) as retrieved from the Allele Frequency Database (ALFRED) (<https://alfred.med.yale.edu/alfred/index.asp>) from 199 populations indicates that the ACE D frequency is high among African ethnic groups. Studies have indicated that the D allele occurs more frequently among African Americans (89%) compared to Asian populations (33%–50%) (Zheng and Cao, 2020). The enormous spread of the ACE II deletion among many African ethnic groups with asymptomatic submicroscopic malarial infections could presumably help to resolve the link between malaria and COVID-19 susceptibility.

Evidence suggests a link between Glucose-6-phosphate dehydrogenase (G6PD) deficiency and increased susceptibility to COVID-19 infection and the severity of the disease (Vick, 2020). Several observations support the hypothesis that G6PD deficiency increases the risk of developing severe COVID-19 (Al-Abdi and Al-Aamri, 2021; Aydemir and Ulusu, 2020). A retrospective chart review on 17 COVID-19 patients from Houston Methodist Hospital, six of which had G6PD deficiency, found prolonged PaO₂/FiO₂ ratio and more days on mechanical ventilation in the G6PD deficient group, along with lower hemoglobin and hematocrit values as indicators of hemolysis (Youssef et al., 2021). Both G6PD deficiency and SARS-CoV-2 compromise the antioxidant system through the same pathways, indicating that the evolutionary antimalarial advantage of G6PD deficient individuals can be a disadvantage in SARS-CoV-2 infection. With high prevalences in Africa, the Mediterranean region and in Asia, this recessive trait affects about 400 million people worldwide. G6PD deficiency was shown to enhance infection of human coronavirus 229E (HCoV 229E) in human lung epithelial cells and G6PD-deficient cells showed increased viral replication and progression of HCoV 229E-mediated cell death. SARS-CoV-2 may have a similar effect (Wu et al., 2008).

The selection pressure exerted by *P. falciparum* has resulted in blood group O being most common in malaria endemic areas (Adegnika et al., 2011), especially in Africa. Blood group O provides a selective advantage against severe malaria through the mechanism of reduced rosetting (Rowe et al., 2007). Recent findings suggest that the ABO blood groups modulate COVID-19 susceptibility and progression, with individuals carrying blood group A being more susceptible to infection and severe clinical manifestations (Severe Covid et al., 2020; Zietz et al., 2020). A recent study has shown that the distribution and modulation of sialic acid-containing receptors on host cell surfaces is crucial, and this is induced by ABO antigens through carbohydrate-carbohydrate interactions, thus influencing the virus spike protein binding to the host cells (Silva-Filho et al., 2020). Given the selective advantage offered by malaria through a wide distribution of blood group O in Africa, reduced COVID-19 susceptibility can be assumed.

Although the World Health Organization (WHO) has provided technical guidance (WHO, 2020d) specifically aimed at prevention of infection, testing, treatment and interventions, several African countries have meanwhile suspended the implementation of vector control activities. This applies especially to the use of insecticide-treated bed-nets and indoor residual spraying. Such a scale-back leaves vulnerable populations, in particular young children and pregnant women, at a greater malaria risk. Taken together, the potential consequences in malaria intervention coverage, morbidity, and mortality during the Covid-19 pandemic in malaria-endemic regions should be addressed in a timely manner.

Tuberculosis and COVID-19

Both tuberculosis (TB) and COVID-19 exhibit overlapping clinical signs and symptoms, but clear differences in their incubation periods and the onset of the disease. Despite being a curable disease, approximately 10 million persons were newly infected by TB in 2019, with an estimated 1.2 million deaths in HIV-negative individuals and an additional 208,000 deaths among HIV-positive individuals (WHO, 2020e). Men accounted for 56%, women for 32% and children for 12% of TB cases in 2019. Among those affected, 8.2% were people living with HIV (WHO, 2020e). The cumulative reduction in incidences from 2015 to 2019 was 9% (from 142 to 130 new cases per 100,000 individuals), with the African Region having made substantial progress (reduction of 16% between 2015 and 2019) (WHO, 2020e). The COVID-19 pandemic threatens to reverse recent progress in reducing the global burden of TB.

COVID-19 is expected to have a significant impact on TB patients, undiagnosed TB patients and TB survivors due to disruption of health services (Saunders and Evans, 2020). Access to diagnostic TB tests will likely be limited because of the stigma associated with coughing or malaise. This stigma might be enhanced during the current pandemic, driving individuals with TB to hide their disease and delaying access to healthcare facilities until disease and infectivity have progressed (Bonadonna et al., 2017). WHO reports that about one third of people living with TB either were not diagnosed or were not reported (WHO, 2019b) and may be major contributors for ongoing transmission with a high risk of related morbidity and mortality. For instance, there were large drops in the reported number of people diagnosed with TB between January and June 2020 (WHO, 2019b). Estimates of global TB detection and care in terms of TB mortality for 2020 indicate a 25% decline in TB case detection, with a predicted 13% increase in TB deaths (an additional 190,000 TB deaths) and an estimated total of 1.66 million TB deaths in 2020, consistent with the number of global TB deaths in 2015 (Glaziou, 2020).

A potential relation between BCG vaccination and COVID-19 is not completely clear. BCG vaccination has been reported to offer protection from infections other than TB (Miller et al., 2020), including viral infections and sepsis (Moorlag et al., 2019). Studies correlating BCG vaccination and reduced mortality due to COVID-19 conclude that countries without a policy of BCG vaccination have been more severely affected compared to countries with universal and long-standing BCG vaccination programs (Miller et al., 2020). However, these comparisons are difficult to validate due to large differences between countries with regard to socioeconomic status, demographics, outbreak periods, number of diagnostic tests performed and test criteria (Escobar et al., 2020).

A meta-analysis using 2932 data sets has shown that TB patients are not more likely to contract COVID-19, but are more prone to develop severe complications of COVID-19 (Gao et al., 2021; Hoai Ta et al., 2020). Clinical TB remains a cause of death related to COVID-19 co-infection.

HIV and COVID-19

The WHO African Region is the region mostly affected by HIV infections with 25.7 million people living with HIV in 2018. With two thirds of the global HIV incidence and >1.1 million new infections per year, the WHO African Region faces a significant challenge in the COVID-19 pandemic (WHO, 2020f). Major progress has been made in recent years in reducing new HIV infections (UNAIDS, 2020). Between 2000 and 2018, new HIV infections decreased by 37% and HIV-related deaths by 45%, with 13.6 million lives saved through antiretroviral therapy (ART) (WHO, 2020f).

Due to strict COVID-19 lockdown measures, individuals may abstain from visiting healthcare facilities for diagnosis and/or treatment, which may cause increased incidences of HIV infections and interruption of ART compliance. The syndemic nature of HIV and SARS-CoV-2 infections in Africa is multifactorial, as it is difficult to understand the actual incidence of COVID-19 in people with HIV and adverse effects may be exacerbated by social and economic inequalities.

As in HIV infection, COVID-19 has had a major impact on women with a higher risk of infection, especially in Africa. In 2019, adolescent girls and young women were estimated to represent 10% of the population in Sub-Saharan-Africa, but are disproportionately affected with 59% of new HIV infections (UNAIDS, 2020; Goga et al., 2020). It was also shown that lesbian, gay, bisexual, transgender and queer (LGBTQ) populations had an increased vulnerability due to COVID-19 and an increased risk for complications due to COVID-19 (UNAIDS, 2020; Fenway, 2020).

In Uganda, maternal mortality increased by 82% between January and March 2020, and there is evidence that rates of HIV diagnoses and of people starting ART and treatment to prevent TB will fall by 75% (Bell et al., 2020; Ntoumi, 2020). Between January and June 2020, data from UNAIDS indicate a sharp reduction in HIV testing during first antenatal care visits in 17 countries (Goga et al., 2020) and equally a reduced treatment access in pregnant women in 15 countries (Goga et al., 2020). Also, until October 22nd 2020, Botswana, South Africa, Sierra Leone, and Togo had not recovered yet to provide routine treatment (UNAIDS, 2020; Goga et al., 2020). Models concluded that fatalities due to HIV infections could increase substantially during the COVID-19 pandemic with interruptions of HIV services in South Africa, Malawi, Zimbabwe, and Uganda (Jewell et al., 2020). These models likely apply to other African countries as well. Also, in countries with high HIV burden, the continuity of ART during the pandemic is a considerable challenge and it is predicted that 40% of those currently on ART are forced to temporarily suspend ART (Jewell et al., 2020). Actions are urgently required in Africa to minimize the widening inequalities in fair access to treatment (Addae, 2021).

It is also evident now that use of lopinavir and ritonavir is not associated with mortality reduction, duration of hospitalization and risk of progression to mechanical ventilation (Consortium WHO et al., 2021; Group RC, 2020; Cao et al., 2020). A systematic review and meta-analysis found increased and frequent adverse events for lopinavir and ritonavir when administered in non-antiviral treatment (Alhumaid et al., 2020). Another postulate was that HIV-infected patients receiving standard anti-HIV drugs might not have an increased risk of SARS-CoV-2 infection (Joob and Wiwanitkit, 2020). An HIV transmission model predicated on implementing HIV tests alongside SARS-CoV-2 testing has the potential to reduce the number of HIV infections substantially in six US cities (PON, 2020).

Policy-makers might consider a combined strategy of health testing and reducing the widespread and long-lasting disruption to ART care, which could cause an increase in the number of deaths that could be saved by interventions. Policy changes could minimize these interruptions through adjustments such as multi-month ART prescriptions.

Conclusion

The indirect effects of the COVID-19 pandemic will severely intensify the burden of HIV infections, malaria and tuberculosis in Africa, where millions of people live with potentially life-threatening diseases. The increase of the disease burden will most likely also apply to non-communicable diseases. Considerable and timely efforts are essential to ensure that cases are not missed and to avoid health care disruptions that would jeopardize the control measures currently in place.

Ethical approval

Not applicable.

Contribution statement

The author TPV collated all literature and wrote the first draft. The authors CGM, PGK, ME and FN contributed to the revisions. All authors have an academic interest. The authors TPV, PGK and FN are members of the Central African Network for Tuberculosis, HIV/AIDS and malaria (CANTAM network). TPV and FN are members of the Pan African Network for Rapid Research, Response, and Preparedness for Infectious Diseases Epidemics Consortium (PANDORA-ID-NET) funded through European and Developing Countries Clinical Trials Partnership (EDCTP).

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Conflict of interest

All authors disclose no conflict of interest.

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