

Perspective

SARS-CoV-2 and Malaria Reciprocal Cross-Immunity

Tareef Fadhil Raham; MOH-Iraq email: tareeffadhil@yahoo.com

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Abstract

Expectations are well known to overestimate Corona Virus Disease of 2019 (COVID-19) burden in all the malaria-endemic regions, especially in Africa. The reported numbers of COVID-19 cases and deaths in Africa were the least. Expectations also overestimated the malaria burden. In April 2020, WHO predicted malaria deaths doubling during the pandemic if actions were not taken. However, the global malaria case incidence remained unchanged and didn't rise, as expected. Furthermore, against all expectations, the global malaria death count did not rise in 2021, and the malaria death count was even averted unexpectedly in Africa. Despite the effect of malaria endemicity on COVID-19 incidence and severity as suggested by the previous literature, the role of exposure to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), in decreasing malaria incidence and severity was not raised yet. Through this perspective, we reviewed and discussed existing data and literature concerning the malaria burden in 2020 and 2021 with the corresponding COVID-19 data to identify whether the spread of COVID-19 disease was related to the lower-than-expected malaria burden. The existence of malaria and SARS-CoV-2 reciprocal cross-immunity was suggested for the first time.

Keywords: Reciprocal Immunity; Cross Immunity; SARS-CoV-2; Malaria; COVID-19.

1. INTRODUCTION

1.1 COVID-19 expectations

The initial cases of Corona Virus Disease of 2019 (COVID-19) were reported in Wuhan, China in December 2019.¹ The World Health Organization (WHO) declared the outbreak a public health emergency of international concern on 30 January 2020.² Cases further skyrocketed causing a global epidemic by March 11, 2020.³ The disease which is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is responsible for more than 6,8 million (M) deaths as of March 23, 2023.⁴⁻⁵ When WHO declared COVID-19 a global pandemic, scientists expected that COVID-19 would be worse in Africa in terms of incidence, prevalence, and mortality.⁶ This is because many African countries are impacted by humanitarian crises, vulnerable population groups, and unique public health challenges. A notable failure of predictive modeling by several bodies on the fate of Africa is evident as time passed.⁷ Africa, contradicting earlier and grim projections, reported a paradoxical profile with the least number of COVID-19 cases and deaths.⁸

In 2021 malaria killed more people in Africa than COVID-19 killed. Malaria, though to aggravate the pandemic in Africa,⁹ became one possible factor for protection against severe COVID-19 in malaria-high-endemic regions.¹⁰ The first COVID-19 case in Africa was reported on 14th February 2020 in Egypt.⁸ Later, cases were reported by

other countries in Africa. By the end of 2021, Africa has progressed in four main waves, with the last wave largely due to the Omicron variant and reported a cumulative of 7,1 million cases and 155,505 deaths.¹¹

Data indicated a less severe disease profile in Africa compared with other regions in the world with proportionally more asymptomatic cases and fewer patients with severe outcomes.¹²

Studies indicated an under-ascertainment of infection based on confirmed cases by surveillance data. A high SARS-CoV-2 seroprevalence is suggesting greater population exposure.¹¹ It was found that SARS-CoV-2 seroprevalence in Africa skyrocketed from 3% in June 2020 to 65% by September 2021.¹¹ The seroprevalence on the continent is 97 times the reported cases. This compares to the global average seroprevalence which is 16 times the number of globally reported cases.

The majority of COVID-19 infections are asymptomatic or mild in nature in Africa while there are a low number of severe cases.^{11,13-14}

As of 31 December 2021 fully vaccinated people amount to 6.6% of the total population indicating a low COVID-19 vaccine coverage.¹⁵

A high COVID-19 seroprevalence, low mortality; and low vaccination coverage indicate potential protection against severe COVID-19 disease in Africa.¹¹

The weak laboratory testing capacity in Africa has been considered an important factor to explain why Africa had the fewest reported number of COVID-19 cases.¹⁶

1.2 Malaria immune cross-reactivity with SARS-CoV-2

Immune cross-reactivity between certain microorganisms and SARS-CoV-2 has been suggested to play an important role in the severity of COVID-19 infection in Africa.¹⁶ Malaria possibly is one of the overlooked microorganisms which led to wrong expectations.

Epidemiological, clinical, and serological studies have suggested that a low occurrence of COVID-19 in malaria-endemic regions was in part attributed to immunogenic reactivity resulting from shared immunodominant epitopes between SARS-CoV-2 *P. falciparum* or cross immunity through innate immune cells responding rapidly by releasing higher levels of cytokines to combat the second unrelated pathogens' invasion. The first infection would be malaria, and SARS-CoV-2 is the second unrelated one.^{10,17-21} Other raised factors explaining the low prevalence and severity of COVID-19 early in the pandemic is the possible immunity cross-reacting with previous BCG and previous latent or active tuberculosis.²¹⁻²⁴

Although the effect of malaria endemicity on decreasing COVID-19 incidence and severity was suggested by the literature, the possible role of exposure to SARS-CoV-2 in decreasing malaria incidence and severity is still not raised yet. We reviewed and discussed the available evidence suggesting the possible role of SARS-CoV-2 in decreasing the malaria burden as far as the recent data indicated an unexpected decrease in malaria trends during 2021, just two years after the pandemic. A discussion on this viewpoint will partially fill the gap in existing knowledge on this subject and trigger further research work in this field.

2. Main Body

2.1 Malaria global situation during 2000-2020

In 2000, nearly 900 thousand people died of malaria. By 2019 this had fallen to 568 thousand deaths. Malaria case incidence per 1000 population at risk reduced from 82 in 2000 to 57 in 2019. The global malaria cases were estimated at 232 million cases in 2019.²⁵

During the COVID-19 pandemic, malaria remained a global health priority.²⁶

The global tally of malaria cases increased to 245 million in 2020 compared to 232 million in 2019. Malaria incidence rates increased excessively in over 50% of the malaria-endemic countries, and malaria mortality rates also increased excessively in around 70% of the malaria-endemic countries. Malaria case incidence (per thousand population at risk) increased to 59 in 2020 compared to 57 in 2019.²⁵ In 2020, malaria deaths increased significantly by 10% compared with 2019, to an estimated 625 thousand.

According to WHO, around two-thirds of the additional deaths (around 47 thousand) were linked to disruption to services during the COVID-19 pandemic.^{17,25}

2.2. Global malaria situation 2021:

Globally, there were an estimated 247 million malaria cases in 2021, a two million increase in the number of cases compared to the number in 2020, with most of this increase coming from countries in the WHO African Region.²⁵ Although cases increased, malaria case incidence did not change from 59 per 1000 population at risk in 2020 instead of the expected 31 cases per 1000 population.²⁵ Against all expectations malaria deaths did not raise in 2021 just a year after the pandemic in Africa. In 2021, the estimated number of malaria deaths was reduced globally by 1% compared to 2020 to an estimated 619 thousand.²⁵ The relative progress in the mortality rate is greater than case incidence. The mortality rate decreased to 14.8 malaria deaths per 100 thousand populations at risk in 2021 with 28 malaria-endemic countries reporting zero malaria deaths in 2021. According to the WHO, this achievement was considered a result of countries' efforts around the world to hold the line against further setbacks to malaria services in 2021.²⁸

2.3 Malaria situation in Africa

There was a vast heterogeneity in the incidence of deaths caused by malaria globally, with the highest malaria burden observed in Africa.

Since 2000, malaria case incidence reduced from 372.6 to 225.5 cases per thousand population at risk in 2019.

Between 2019 and 2020, estimated malaria cases in the WHO African Region increased from 218 million to 232 million. The case incidence per 1000 population at risk decreased in 2019 from 373 to 225, increased to 234 in 2020, and declined to 229 per thousand population in 2021. Between 2000 and 2019, the malaria death count in the WHO African Region, reduced from 841 thousand to 544 thousand which represents a 62% reduction. This represents a reduced mortality rate from 148.4 to 56.3 per 100 thousand populations.

In 2020, the mortality rate increased to 60.4 per 100 000 population (due to disruptions in malaria programs) before decreasing in 2021 to 58.2.²⁵

In 2020, African countries suffered the most from malaria. Multiple factors have co-driven disruptions of malaria control programs during COVID-19 leading to an increase in malaria burden in Africa in 2020, leading to a significant negative impact on malaria control.²⁹

In 2021, the WHO African Region accounted for about 95% of cases and 96% of deaths globally; 78.9% of all deaths in this region were among children aged under 5 years.

In 2021, the case incidence declined to 229 per thousand population.²⁵ The later reduction was reported despite increased cumulative COVID-19 cases (7,1 million on 29 December 2021) and opposite to all expectations. Furthermore, in 2021, while malaria cases increased to 234 million, malaria deaths decreased to 593 thousand.²⁵

The decrease in malaria case index, mortality rate, and death count in 2021 possibly represents in part the SARS-CoV-2 exposure effect as the pandemic is late in Africa, in addition to success in malaria control programs. Despite these reductions, 2019 levels were not achieved. This possibly indicates an existing level of disruption in malaria programs in 2021.

On 29 December 2021 the reported COVID-19 cases in the Republic of South Africa 3,4 million cases (48%,) were the majority of the cases in the WHO African region from a single country.¹⁶ At the same time South Africa's malaria incidence was as low as 0.5 per thousand population. On the other hand, the Republic of Chad reported the least incidence of COVID-19¹⁶ while its malaria incidence was as high as 206.4 per thousand population³¹. These two examples may reflect the existing inverse relation between malaria and COVID-19 levels.

3. DISCUSSION

3.1. Failure of malaria expectations

In April 2020, WHO predicted a doubling of malaria deaths during the pandemic if no actions were taken.^{9, 32-33} Despite the impact of COVID-19, malaria deaths number remained stable in 2021 with an overall decrease in mortality rate²⁵, the expected case incidence of 31 cases per 1000 population was not achieved; and "The predicted doubling in malaria deaths was averted," according to Kenya's President Uhuru Kenyatta, who chairs the [African Leaders Malaria Alliance](#).³⁴ This was considered an unpredicted success in malaria control programs.

It looks that both malaria and COVID-19 were missed in expectations and malaria showed a reverse trend in many regions against all expectations. As far as there was a decrease in malaria mortality and incidence rates, we raised a possible role of reciprocal cross-reacting immunity. Immunity towards malaria may be created after exposure to SARS-CoV-2 creates immunity by mechanisms possibly similar to that suggested to be created by malaria towards SARS-CoV-2.

During 2020 there was a global increase in malaria cases and deaths mainly in Africa. These were attributed to interruptions caused by the COVID-19 pandemic. During 2020 (the first year of the pandemic), herd immunity against COVID-19 was low, especially in Africa. A reduction in malaria case index and mortality in 2021 despite interruptions caused by the pandemic makes us think about the possible roles of the widespread COVID-19 cases. The suggested reciprocal immunity together with improved malaria program responses; and possibly yet not determined factors might explain why countries with fewer reported COVID-19 cases reported the highest number of malaria cases and vice versa.

Although this needs validation, possibly SARS-CoV-2 preexisting immunity due to previous exposure cross-reacts with malaria given a trained heterogeneous immunity against malaria infection.

Models that, by design, disregard the key elements driving outcomes in the real world fail to predict the outcome. Neglecting the reciprocal effect (in malaria-endemic regions and possibly where malaria is recently eliminated) between malaria and COVID-19 might be the cause of the failure of predictions.

3.2. Failure of malaria expectations for China

China has made large strides toward eliminating malaria. China was certified malaria-free in 2021 after reporting 4 consecutive years of zero indigenous cases.³⁵ China's official

COVID-19 death toll for the entire pandemic remains strikingly low. The differences between China's official figures and researchers' expectations led researchers to consider this as a vast undercount.

The estimates for the official cumulative COVID-19 deaths per 100,000 people in China is 7.16,³⁶ while the death count estimates obtained from estimates is 68.4-110.³⁷⁻³⁸

The endemic area of malaria in China has been historically restricted to Yunnan and Hainan provinces since 1998 till malaria elimination in 2021.³⁹ Yunnan's COVID-19 deaths/1M population was 0.04 (as of 5 July 2021) and Hainan's COVID-19 deaths /1M population was 0.64 (as of 5 July 2021).⁴⁰⁻⁴¹

As of November 2020, the COVID-19 deaths /1M population in Hubei was 76.13⁴⁰ which is higher than that of Yunnan and Hainan. In Hubei, malaria cases decreased since 2008. A total of 429 malaria cases were reported in 2010.⁴² Plasmodium vivax malaria cases accounted for most malaria cases. Hubei Province has not had any indigenous cases of P. falciparum malaria since 1963. No indigenous malaria cases have been reported in Hubei Province since 2013.⁴²

The last indigenous cases of Plasmodium falciparum and Plasmodium vivax in Yunnan were registered in 2015 and 2016. Both type species of plasmodium and elapsing a long time since elimination possibly explain the high burden in Hubei.^{18,21}

While China is possibly a good prototype to look for past malaria exposure affecting later COVID-19, Africa is a good prototype to look for the reciprocal effect of malaria and COVID-19 as malaria is still an ongoing problem there.

3.3. COVID-19 deaths versus malaria case incidence in the WHO regions

In December 2021 death number caused by COVID-19 in WHO regions was (from high to low) 2 411 818 (44%) in the Americas, 1 674 758 (31%) in Europe, 721 940 (13%) in South-East Asia, 316 141 (6%) in Eastern Mediterranean, 156 515 (3%) in west pacific and the least number of deaths was in Africa which accounted 156 451 (3%).³⁰

Malaria case incidence per 1000 population at risk in the WHO Regions except for The Americas was (from lower to higher): The European Region has been free of malaria since 2015²⁵, The Western Pacific Region 2 in 2021, The South-East Asia 3 in 2021, The Eastern Mediterranean Region (including Sudan) 12, and The African Region 229 (the highest).²⁵

Except for the west pacific (which includes China), regions with high COVID-19 deaths have low malaria case incidence and vice versa.

3.3.1 The WHO Region of the Americas

In the WHO Region of the Americas, malaria cases were reduced by more than half in 2020 (to 223 thousand cases) compared with 2019, and further in 2021 to 205 thousand cases.²⁵ This decrease was thought to be due to restrictions on movement during the COVID-19 pandemic.²⁵ Such an explanation did not explain the high COVID-19 attack rate in this region. Possibly COVID-19's early high attack rate contributes to this malaria reduction.

[Peru](#), with a total population of 32 million people, as of March 23, 2023, reached 4.49 million confirmed [COVID-19](#) cases and 219.6 thousand deaths. The reported mortality rate accounts for 6450 deaths/ M.⁴ Peru sustained the highest [COVID-19 pandemic death rate](#) in the world since the early weeks of the pandemic.⁴⁴ A remarkable decline was observed in the number of malaria cases in the Loreto region of the Peruvian Amazon. The reduction was 20% in March, 44% in April, 88% in May; and 99% in June. The number of malaria cases was just 35 malaria cases in the last week of June. These reductions are striking for the region known for the highest number of cases reported before the pandemic.⁴⁵ At the epidemiological week 26, 2020 COVID-19 deaths in Loreto exceeded 1,768 deaths.¹¹ Peru's health ministry announced on 13 August 2020, that Peru had exceeded 0.5 million confirmed cases, and 25 thousand deaths were recorded. Furthermore, in 2021 malaria cases in Peru decreased to 1.8 per 1.000 population at risk⁴⁴ compared to 2.6 cases per 1 000 in 2019.⁴⁶ The substantial reduction in malaria number of cases in Peru between 2019 and 2020 was (-22 000).²⁵ Over the same period substantial reductions in cases were seen in places with high COVID-19 like Brazil (-17 000) (3,247 COVID-19 deaths /M); and Colombia (-17 000) (2,769 COVID-19 deaths /M).^{25,47} Estimated malaria cases more than doubled in 2021 compared with 2019 in places with lower COVID-19 burdens like Honduras (1,087 COVID-19 deaths /M) and Panama (1,936 COVID-19 deaths).^{25,47}

We conclude that the early decrease in malaria fatality and case index in certain malaria regions in 2020 and the latest (2021) decrease in malaria mortality rate and case index is possibly due to increased seroprevalence towards the SARS-CoV-2 virus in South America at early times of the pandemic in 2020 and in Africa at later times in 2021 .¹¹

3.4. Reciprocal immunity dilemma in children

Seroprevalence studies, indicated lower SARS-CoV-2 seroprevalence for children 0–9 years in Africa¹¹ while most of the malaria cases and deaths were children below 5 years of age.⁴⁸ As adults get malaria in early childhood we expect lower COVID-19 symptomatic / asymptomatic cases and deaths in adults previously exposed to malaria compared to non-exposed adults. As COVID-19 is less prevalent in childhood we expect its influence on malaria incidence reduction among children to be less than malaria's influence on COVID-19 incidence reduction among children. In the WHO African Region, 78.9% of all malaria deaths were among children aged under 5 years which is slightly higher than the global figure which is around 76%.²⁵ This indicates that children aged under 5 years in the African region are still more susceptible to death from malaria than older age groups. This may be attributed in part to lack of immunity towards malaria among children aged under 5 years compared to adults who gain this immunity through previous exposure (s) / or through possible cross-immunity created by exposure to SARS-CoV-2 or other infections.

CONCLUSIONS

As far as the only previously suggested evidence is the mala-

ria effect on decreasing the COVID-19 burden, we address her that the COVID-19 effect is the first time to be suggested (as far as we know).

Although additional in-depth studies are required to confirm this hypothesis we suggest at this level of evidence that a cross-immunity is reciprocal between malaria and SARS-CoV-2 each one can protect against the other.

List of abbreviations

M: million

COVID-19: Corona Virus Disease of 2019

SARS-CoV-2:severe acute respiratory syndrome coronavirus 2

WHO: The World Health Organization

Declarations

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- Consent for publication: 'Not applicable'
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