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Is Laps of Time Since Malaria Elimination a Factor in COVID-19 Mortality?

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ABSTRACT

Malaria can elicit a non-specific immune response against viral, bacterial and other malarial and non-malarial infections. Early in this pandemic suggestions were raised for possible role of cross immunity induced by malaria or other agents against SARS-CoV-2 severity. A possible role of heterogeneous immunity generated by previous malaria infection was suggested to explain part of diversity in COVID-19 mortality among various countries. This study was designed to examine this hypothesis by looking for possible statistical relation between malaria elimination date and COVID-19 mortality. Sixty -nine malaria-free countries with a total population of 1 million or more were enrolled in this study using robust statistical tests which include: Mann-Whitney Test, Kendall's-τ coefficient test and receiver operation characteristic - (ROC) curve analyses. Results showed that there was a significant negative association among studied marker (COVID -19 deaths/million inhabitant , and date of elimination of malaria (using Kendall's-τ Correlation Coefficient test). There was a significant positive association between COVID-19 mortality and duration of time since the time of malaria elimination. With a cutoff point of 15, countries that eliminate malaria during the last 15 years had reduced median COVID-19 mortality, while countries that eliminate malaria more than 15 years ago there is high COVID-19 median mortality p value <0.05) . Receiver operation characteristic - (ROC) curve, was used to support these findings (P value <0.05). The author of this article suggests that a correlation exists between malaria elimination duration and mortality due to COVID-19.

1. Introduction

Periodic fevers of malaria are found throughout recorded history beginning in the first millennium BC in Greece and China (Neghina, et al., 2010). Until the mid-nineteenth century, malaria was endemic in most countries across the globe (Shretta, et al., 2017). During the 20th century, many countries eliminated malaria, and in 1955 WHO launched the Global Malaria Eradication Program (Wernsdorfer &, Kouznetzov, 1980). It is well known that malaria has a cross- protection effect for some bacteriae (Nelson, 2015; Baluku et al., 2019; Page, et al., 2005; Murphy, 1980; Perez-Mazliah & Langhorne, 2014). It was also known that malaria has a cross protection effect for a some bacterial viral infections (Waitumbi et al ,2010; Rooth & Bjorkman, 1992).

It has been already suggested by a number of studies that priming the response to SARS-CoV-2 through pre-existing T cell immunity (Cross-Reactive trained Immunity) possibly induced by common cold coronaviruses (Beretta, et al., 2020) or past latent TB (Al-Momen, 2020; Raham,2020b, 2021a, 2021c) or BCG (Cernovsky, 2020; Raham, 2020a). The concept of trained immunity was back to 2011 (Netea et al., 2011). It was speculated that quantitative enhancement of the innate immune responses and phenotyping changes in the innate immune cell subpopulations play an important role in the mechanism of trained immunity (Alsulaiman, et al., 2020). It is believed that COVID-19 pandemic is deterministically driven by multiple drivers (Kubota et al., 2020) for example in one study found that BCG vaccination explains 26% of variance in cases of COVID-19 per Capita (Cernovsky, 2020).

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1.1. Literature Review

Studies suggested that malaria-endemic areas appear to carry low risk for catching SARS-CoV-2 Recent studies suggested that malaria-endemic areas appear to carry low risk for catching SARS-CoV-2 and vice versa (Ahmed, 2020; Banerjee & Saha, 2020; Napoli & Nioi, 2020). Gomes et al. (2014) found a relationship between antiphospholipid antibodies and parasitemia levels in malaria infected. Coronavirus 19 presents different glycoproteins that speculated to be recognized by the antibodies produced in malaria and could protect by virus infection or induced a milder disease (Parodi & Cozzani, 2020). Furthermore more recent study founded that *Plasmodium falciparum* cumulative exposure induces epigenetic reprogramming of monocytes/macrophages toward a regulatory phenotype that mitigated inflammatory responses during subsequent *Plasmodium falciparum* exposure. The study suggested that past malaria exposure could attenuate monocyte-associated immunopathology induced by other pathogens such as SARS-CoV-2 (Page, et al., 2005; Guha, et al., 2020) .

On the same context, a study found there was significant correlation between incidence of malaria and mortality due to COVID-19 in malaria endemic areas (Raham, 2021b). We considered in this study date of elimination of malaria as possible contributing factor for such variances. We looked here for association of date of malaria elimination with COVID-19 mortality. Our hypothesis stands on possible heterogeneous cross herd immunity generated by malaria in past.Given our current understanding of malaria nonspecific possible cross reacting immune mechanism and by analyzing current epidemiological data, this study aims to identify a possible correlation between the malaria elimination date and mortality associated to COVID-19 infections.

2. Materials and Methods

It was not appropriate or possible to involve patients or the public in this work given that patients were not involved as far as we used publically published morbidity and mortality statistics. We selected countries that have achieved malaria elimination or added to the supplementary list by WHO.

According to WHO Malaria elimination is the interruption of local transmission (that is, reducing the rate of malaria cases to zero) of a specified parasite in a defined geographic area. We selected countries granted certification of malaria elimination by WHO (as far as a country has proved, beyond reasonable doubt, that the chain of local malaria transmission by Anopheles mosquitoes has been interrupted nationwide for at least three consecutive years). We select also free of malaria countries listed in supplementary list by WHO. The supplementary list contains countries where malaria never existed or disappeared years or decades ago and where full WHO certification of malaria elimination is not needed.

Countries and territories with less than 1 million populations are excluded. Publically available references for data are available as attached supplement. COVID-19 deaths/million (M) reported as it was in 1st of September 2020 as it is in : WHO Coronavirus (COVID-19) Dashboard Total countries chosen were 69, distributed among that categories status as shown in attached. All statistical operations were performed through using the ready-made statistical package SPSS, ver. 22. We used a Kendall's-τ Correlation Coefficient (a non-parametric rank correlation test) to assess statistical associations based on the ranks of the data. Using iteration method, we found a cut-off point time duration since elimination of malaria of 15 years as time that divide the countries in two different groups. To test the null hypothesis, we used then Mann-Whitney test which compares the medians from two populations.

Finally, we used receiver operation characteristic - (ROC) curve, to discriminate between different two categories status of malaria elimination periods by (COVID-19 deaths/million) and to assess significant associations according to best identified cut off point.

3. Results & Discussion

Tables (1) represents "Kendall's-τ Correlation Coefficient" and P-values for studying the amount and the direction concerning relationships among the studied markers. Results showed that a strong relationship was represented among studied marker (COVID -19 deaths/m, and date of elimination of malaria by negative way.

Table 1
Kendall's-τ Correlation Coefficient" for the sample

Markers	Correlation Coeff. and P-value	Date of elimination of Malaria
COVID -19 Deaths/M	Correlation Coefficient	-0.175 *
	Sig. (2-tailed)	0.046
	No.	69
* Correlation is significant at the .05 level (2-tailed).		

Cut-off point for duration of time since elimination of malaria was found to be 15 years (using iteration method). This cutoff significant point classifies countries into those with short period (≤ 15year) and those with long periods (> 15 years) (table 2, table 3 and appendix 1).

Tables (2) represents summary statistics concerning (COVID -19 deaths/M) concerning studied groups of time periods since malaria elimination, these statistics include (5% trimmed mean, median, minimum, maximum readings, range, and interquartile range), in addition to the significant comparisons between time periods since malaria elimination using Mann-Whitney Test. Results showed that with smaller the number of malaria elimination period (the shorter the time), the lower the number of COVID -19 deaths, and vice versa. This finding was associated with significant difference between short and long periods at P<0.05.

Table 2
Descriptive Statistics of (COVID -19 Deaths/M) and testing of all probable combinations due to elimination of malaria periods for studied countries

COVID-19 deaths /M Statistics	Malaria country group (COVID-19 deaths /M) according to malaria elimination time	
	Short	Long
5% Trimmed Mean	75	185
Median	47	108
Minimum	0	4
Maximum	469	853
Range	469	849
Interquartile Range	97	292
Mann-Whitney Test	Z = -1.962	
P-value	P=0.04981 (S)	

HS: Highly Sig. at P<0.01; S: Sig. at P<0.05; NS: Non Sig. at P>0.05.

Receiver operation characteristic - (ROC) curve, was used to discriminate between different two categories status of malaria elimination periods by (COVID-19 deaths/million) marker (Fig 1 and table 3). Statistical results concerning (COVID -19 deaths/M) in light of studied groups of countries classified according to duration of time since malaria elimination date showed that countries that got rid of malaria for longer periods had more deaths caused by COVID -19, with asymptotic significance at P<0.05.

Table 3
ROC – Curve classifying time period groups since malaria elimination date by (COVID -19 Deaths/M) Marker

Period of elimination of Malaria	Marker	Area	Std. Error	Asymp. Sig.	Asymp. 95% C.I. L.b.	Asymp. 95% C.I. U.b.
Short X Long	COVID -19 Deaths/M 2/August	0.638	0.067	0.04984 (S)	0.507	0.768

S: Sig. at P<0.05.

Figure (1) represents graphically ROC curve plot for studied COVID -19 deaths/M) marker in relation with time periods of elimination of malaria.

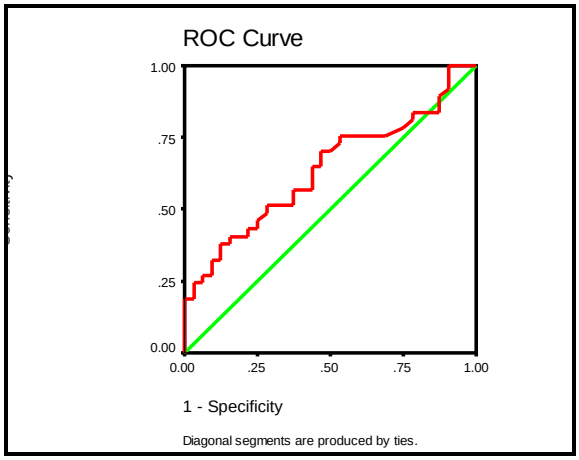

Fig. 1. ROC Curve plot for studied COVID -19 deaths/M on 2/September 2020) marker in relation to periods of elimination of malaria

In order to obtain a detailed view that reflects the true behavior of the recorded deaths as a result of COVID -19 influenced by the effect of both duration times of malaria elimination groups, Stem-Leaf graphical plots method was used to illustrate this very accurately, as represented in figure (2).

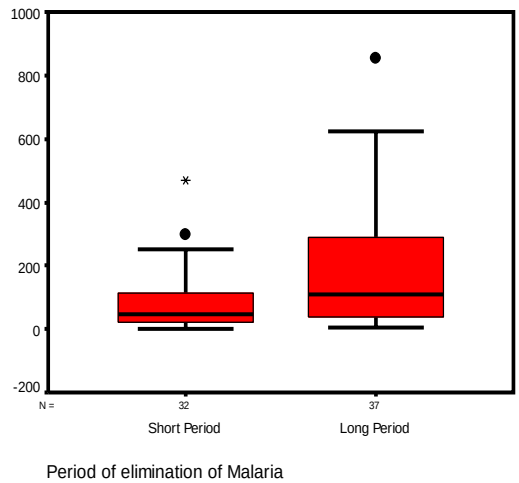

Fig. 2. Stem-Leaf plots of (COVID -19 deaths/M as it was in 2nd of September 2020) versus duration of time period since elimination of malaria.

Possibly malaria through inducing trained immunity provides non-specific protection. This may explains (in part) variances in COVID-19 mortalities among different countries, as far as populations among countries recently eliminating malaria have statistical correlation with decreased mortality in comparison to higher mortalities among population in countries which eliminate malaria for long time. It is well known that immunity wanes with time including immunity generated by vaccines (Cohen, 2019). The finding of association between duration of time for malaria elimination and COVID-19 mortality noticed in this study (tables 1,2 and 3 and figure 1) might be due waning immunity generated by malaria cross reacting to SARS-Cov-2.

Due to the fact that the surveyed data were discrete and have an ordinal scale, the methods of description and inferences were not parameterized therefore "Kendall's-τ correlation coefficient" was used to study the amount and the direction relationships among the studied markers. It yielded significant association in negative way denoting associated role of date of malaria elimination to COVID-19 mortality.

Also "Mann-Whitney test" was used for testing the equality of means in two independent samples. Results showed that smaller the number of malaria elimination period (the shorter the time), the lower the number of COVID -19 deaths, and vice versa. This was also confirmed by (ROC) curve statistical analyses and illustrated by "Stem-Leaf" plot (figures 1 and 2). We have shown that cut off time differentiating mortality produced by COVID-19 across countries were correlated with a country's time of malaria elimination.

For the correlation to be translated into causation, the mechanisms of malaria induced trained immunity should be consistent with the findings in human clinical studies through randomized controlled trials which are required to determine an immune response develops that protects against COVID-19. Since this is not yet definitively settled, it is presumptive and based on limited evidence to conclude that malaria confers cross immune response against SARS-COV-2 at this time. Statistical association per se does not necessary mean causation since this needs further clinical and preclinical studies to establish causation.

It was known for some viruses, the first infection can provide lifelong immunity; but for seasonal coronaviruses it was said that, protective immunity is short-lived (Edridge, et al., 2020). Regarding SARS-CoV-2- limited early data suggests that most patients seroconvert for SARS-CoV-2-specific IgG within 2 weeks. While the long-term duration of antibody responses is unknown. Evidence from SARS-CoV studies suggest SARS-CoV-specific IgG is sustained for one to two years and declines thereafter (O Murchu, et al. , 2021). Nevertheless there is a lot of debate existing nowadays regarding immunity followed by primary SARS-CoV-2 infection and whether immunity following infection last for a long period or not and a lot of concerns also raised regarding the severity of reinfection (Iwasaki, 2020). .

Reinfection as discussed above is a matter of immunoglobulin. The severity of the disease is largely related to hyper drive of innate response. This hyper drive response is said to be by related to trained immunity induced by previous infection caused by related or unrelated microorganisms (Netea, et al., 2020). We suggest her that it is possible for innate immunity triggered by malaria and cross react against SARS-COV-2 to last for long time (possibly for 15 years). The influence of time duration of cessation of BCG vaccination programs was also statistically positively associated COVID-19 mortality in countries ceased implementing BCG vaccine in previous study (Raham, 2020a). Our suggestion is that when cross immunity develops by these infections this will lead to certain degree of herd immunity. In herd immunity , immune individuals are less likely to contribute to disease transmission, disrupting chains of infection, which stops or slows the spread of disease (Merrill, 2013) .

Conveying this information (if proved) into clinical practice might seems be difficult for first instance as far as malaria is a killer disease and eradication of reservoir of infection through treating subclinical cases is essential (The malERA Consultative Group on Drugs, 2011), on the other hand addressing such findings will lead us to understand the possible role of malaria against SARS-CoV-2 and a possible role of longstanding trained immunity response (as we suggest) in addition to role of humoral immunity which may last just for short time as preliminary data suggests. According to evolution theory new strain of coronavirus might get evolution (in part) as response to occupy what is called (vacated niche). This suggested vacated niche might be created by factors related to malaria or other factors like low TB prevalence (including low latent TB and absence of BCG vaccination).

There is a lot of concerns about the role of malaria, the role of TB , BCG and other possible biological factors like other vaccines or infections in preventing emergence of SARS-Cov2 and ameliorate its grave consequences. Possibly eradication of malaria, and TB and other killing infections with wide use of antibiotics might have a role in creating a suitable environment for emergence of new stain of coronavirus that occupy the niche created in absence of heterogeneous antibodies suggested to protect humans against SARS-CoV-2 infection. These factors according to evolutionary hypothesis are part of natural environment of an organism "selects for" traits that confer a reproductive advantage, causing evolutionary change (Darwin, 1859; Gregory, 2009). Natural selection is a cornerstone of modern biology. That is to say the natural environment seems to be (favored or selected for) SARS Cov-2 when these factors are present, while in the presence of high endemicity of malaria or TB (BCG or latent TB) or other possible biological factors, the environment is said to be (un favored or selected against) SARS-CoV-2.

According to incumbent replacement theory which is an evolutionary mechanism, proposed in 1991 by Rosenzweig and McCord (1991), a well-adapted species (the incumbent) becomes extinct, due to a chance combination of adverse factors. Is that was true for SARS-Cov-2 or other possible serious strain in the presence of high malaria incidence and high TB prevalence during previous centuries? We recommend here eradication by live vaccines would be suitable alternative breaking the cycle of transmission of the disease. Vaccines participate in building essential specific herd immunity and essential cross reacting immunity. So we think possibly presence of malaria and TB in nature prevent certain viruses from evolution and species generation. So specifically speaking vaccination against malaria may be better than other means of elimination or eradication as far as it could build immunity as natural infection.

4. Conclusions

Malaria might have cross immune protective effect in reducing COVID-19 mortality. Such possible effect possibly is not short lived and might last for many years (a minimum of 15 years). We recommend further studies including clinical and preclinical trials to find relation of malaria herd immunity to COX-CoV-2 infection.

- There is no “Conflict of interest” to be declared
- No findings were received.

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Competing Interests

The authors have declared that no competing interests exist.

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