

COVID-19 and Malaria: A Fatal Attraction for SARS CoV-2?

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Received: 11 Jun, 2020 | Accepted: 22 Jun, 2020 | Published: 26 Jun, 2020

Citation: Harris RE, Rosemurgy AS (2020) COVID-19 and Malaria: A Fatal Attraction for SARS CoV-2? J Epidemiol Public Health Rev 5(2): dx.doi.org/10.16966/2471-8211.194

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Abstract

We examined trends and differences in the average cumulative rates of COVID-19 cases and deaths per million (incidence and mortality rates) among 11 Asian nations where malaria is endemic (China, Hong Kong, South Korea, Thailand, Vietnam, Cambodia, India, Pakistan, Malaysia, Indonesia and the Philippines) and compared these trends and differences to 11 western nations (United States, Canada, Great Britain, Spain, Italy, Germany, France, Portugal, Netherlands, Switzerland and Austria) during the five month period, 1/1/2020-5/31/2020. The mean rates of incidence and mortality for the two sets of countries diverge markedly and as of May 31, 2020, the incidence and mortality rates for Asian countries (130 per million and 3.6 per million, respectively) were 1/27th and 1/89th of the corresponding rates for North American and Western European countries (3,481 per million and 321 per million). In contrast, annual incidence rates of malaria are negligible in North America and Europe whereas malaria is endemic in Southeast Asia (3.5 per 1,000). Chronic infections by malarial plasmodia induce interferons and neutralizing antibodies with proven impact against infection by the corona viruses responsible for SARS, MERS and COVID-19. Therefore, there may be natural immunity against infection by SARS CoV-2 in populations that have a longstanding history of widespread exposure to malarial infections. Such populations may be a valuable resource for development of effective vaccines and serological agents for the prevention and therapy of COVID-19.

Keywords: SARS CoV-2; COVID-19; Malaria; Interferons; Neutralizing Antibodies; Incidence; Mortality

Introduction

In a preliminary study, we found huge differences in the mean incidence and mortality of COVID-19 between countries of South Asia *versus* those in North America and Western Europe [1]. As of May 4, 2020, the average incidence rate (83.7 per million) and the average mortality rate (2.24 per million) in 11 Asian countries were approximately 1/34th and 1/118th, respectively, of the corresponding values reported by countries in North America and Europe (2,878 per million and 265 per million, respectively). In contrast, the annual incidence of endemic malaria shows the reciprocal pattern: rates are negligible in North America and Europe and relatively high in Southeast Asia.

In this report, we examined patterns of SARS CoV-2 infections in countries of each of these regions and the reciprocal pattern in the annual incidence rates of malaria. Our results are current to May 31, 2020.

Methods

Methods were similar to our initial epidemiologic study [1]. We abstracted rates of tests for COVID-19 infection, rates of positive tests (unadjusted incidence rates), and COVID-19 death rates (unadjusted mortality rates) for eleven Southeastern Asia countries (China, Hong

Kong, South Korea, Thailand, Vietnam, Cambodia, India, Pakistan, Malaysia, Indonesia and the Philippines) from the Worldometers website [2] for comparison with eleven countries of North America and Europe (United States, Canada, Great Britain, Spain, Italy, Germany, France, Portugal, Netherlands, Switzerland and Austria). Asian countries were selected due to their proximity to the epicenter of the COVID-19 pandemic in Wuhan, China. Means of the rates for each set of countries were calculated with 95% confidence intervals and mean differences checked for statistical significance by t-tests. We also estimated crude case fatality rates for each country (unadjusted case fatality=death rate/case rate) and tested the difference in mean case fatality for each set of countries. Mean rates for the Asian and Western countries were computed at weekly time intervals during 3/1/2020-5/31/2020 and plotted over time. Trends and differences in weekly rates were modeled by fitting S curves to the data using the logistic function.

Results

The mean incidence and mortality rates reported for COVID-19 show a sharp divergence in countries of Southeastern Asia compared to North America and Europe. As shown in the table 1, the average incidence rate of cases (130.4 per million) and the average mortality rate (3.6 per million) in the Asian countries through May 31, 2020,

were approximately $1/27^{\text{th}}$ and $1/89^{\text{th}}$, respectively, of the corresponding values reported by countries in North America and Europe (3,480 per million and 321 per million, respectively, $P < 0.001$). For these same countries, the average frequency of positive tests among all tests for COVID-19 in Asia (1.76%) was 74% less than the corresponding frequency (6.85%) in North America and Europe ($P < 0.01$). Similarly, the mean case fatality among Asian countries (2.76%) was 70% less than the corresponding estimate (9.22%) for countries of North America and Europe ($P < 0.01$). Since China did not report the number of tests conducted, we also calculated rates and differences with the China data excluded, but found little change in the results (Table 1).

The Table also includes recently reported annual incidence rates of malaria for the countries of North America and Europe *versus* Southeast Asia [3]. Clearly, the incidence rates of malaria are inversely related to the incidence and mortality of COVID-19, e.g., COVID-19 rates are relatively high and malaria rates are negligible in North America and Europe whereas COVID-19 rates are relatively low and malaria rates high in Southeastern Asia.

Figure 1 shows the trends and marked differences in the mean COVID-19 mortality rates for the 11 countries of Southeastern Asia *versus* those of North America and Europe during 4/1/2020-5/31/2020. Note that in order to plot these rates on the same chart, the rates for the

countries of Southeastern Asia were expressed per 10 million whereas rates for the countries of North America and Europe were expressed per million. Throughout the time period covered, the average mortality rate for the countries of North America and Europe was approximately 90-fold higher than the countries of Southeastern Asia. Based on the best fitting logistic functions (S curves) shown in Figure 1 for each set of data, the mean COVID-19 mortality is projected to maximize at approximately 60 per 10 million for the Asian nations and 350 per million for the North American and Western European nations by the end of June, 2020.

Discussion and Conclusion

Our results show marked divergence in the incidence and mortality of COVID-19 between Southeastern Asian countries and North American/Western European countries. Malaria is endemic in those nations with low rates of COVID-19 but is negligible in nations with high rates of COVID-19. The difference in mortality is particularly striking as COVID-19 death rates are approximately 90-fold higher in non-endemic nations compared to those that are endemic for malaria.

Other investigators have also begun to examine COVID-19 rates in countries endemic for malaria compared to non-endemic countries. Early preprints and preliminary reports of these studies are in

Table 1: Cumulative COVID-19 rates compared to the incidence of malaria in countries of Southeastern Asia, North America and Europe, 12/01/2020-5/31/2020.

Country	COVID-19 Tests/M	COVID-19 Cases/M	COVID-19 Deaths/M	Malaria Cases Incidence/1,000
North American & European Countries				
United States	52,326	5,501	319	0
Canada	43,334	2,391	188	0
Italy	63,249	3,848	551	0
Spain	76,071	6,124	580	0
Germany	47,193	2,189	103	0
France	21,217	2,890	441	0
Portugal	78,030	3,187	138	0
Great Britain	61,474	4,021	566	0
Netherlands	20,380	2,711	348	0
Switzerland	45,980	3,568	222	0
Austria	49,826	1,859	74	0
Mean (95% CI)	50,825	3,481 (2,649-4,312)	321 (203-439)	0
Southeastern Asian Countries				
China	580	58	3	<0.1
Hong Kong	27,087	145	0.5	<0.1
South Korea	17,767	224	5	<0.1
Malaysia	17,111	242	4	0.1
Philippines	3,176	165	9	0.3
Pakistan	2,481	315	7	4.9
Thailand	5,380	44	0.8	0.8
Viet Nam	2,827	3	0.1	0.1
Cambodia	1,222	7	0.2	18.4
Indonesia	1,183	97	6	5.8
India	2,710	135	4	7.7
Mean (95% CI)	7,411	130.5 (68-193)	3.60 (1.7-5.5)	3.5 (0.2-6.8)
Excl. China (95% CI)	8,094	134.7 (70-205)	3.66 (1.6-5.7)	3.8 (0.2-7.4)

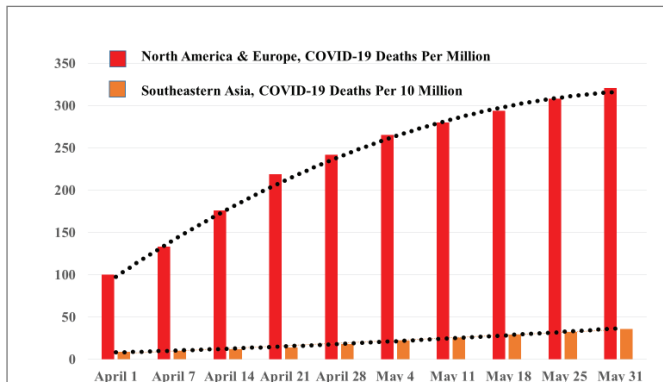


Figure 1: Mean COVID-19 mortality in countries of Southeastern Asia versus North America and Europe, 4/1/2020-5/31/2020.

agreement with our findings indicating that malaria-free populations have markedly higher rates of COVID-19 than nations plagued by endemic malaria [4-7].

One hypothesis advanced to explain the low COVID-19 rates in populations' endemic for malaria is their widespread use of anti-malarial drugs that have anti-viral effects. For example, some studies have found that the anti-malarial agent, Hydroxychloroquine (HCQ), has therapeutic benefit for patients with COVID-19 [8]. Since this relatively inexpensive anti-malarial drug was widely used for many decades in the geographic hot zones of malaria in Southeast Asia, it has been suggested that HCQ may have current chemopreventive impact against novel viral infections such as SARS CoV-2 [4,5]. However, due to the evolvement of chloroquine-resistant strains of malarial plasmodia, HCQ prophylaxis has largely been replaced by other more effective drugs and HCQ is not currently in widespread use in the general populations of these nations [9]. Furthermore, HCQ is a zinc ionophore, and the anti-viral effects of HCQ are primarily due to the intracellular inhibition of viral replication by zinc ions [10]. Since a large portion of South Asian populations suffer from zinc deficiency [11], it is therefore unlikely that HCQ would be an effective chemopreventive agent against SARS CoV-2 in these populations.

A more likely hypothesis is that repeat malarial infections that are widespread in South Asian populations create immunocompetence not only against malaria, but also against novel viral infections. It is well known that malaria induces interferons with proven impact against infection by certain viruses. Molecular studies from multiple laboratories have found that interferons released by lymphocytes is a normal immune response to infection by multiple strains of malaria, and that these same interferons have both *in vitro* and *in vivo* effects against the coronaviruses responsible for SARS, MERS and COVID-19 [12-15]. Repeat malarial infections also induce the development of persisting antibodies that neutralize a broad profile of merozoite antigens, and neutralizing antibodies have recently been noted to have effects against SARS CoV-2 and other coronaviruses [16,17].

While it can be argued that the inverse association of COVID-19 and malaria may primarily reflect disparities in demographics, testing, reporting, and infection control, the potential for biological effects must also be considered. The epidemiological data characterizing the current COVID-19 pandemic combined with the international pattern of malaria and molecular findings regarding the long term immune impact of repeat malarial infections can be interpreted to support the hypothesis that there may be natural immunity against COVID-19 in

populations that have a longstanding history of widespread exposure and acquired natural immunity to malarial infections. Specifically, the majority of individuals in these populations may have high levels of circulating interferons, neutralizing antibodies, and other factors that enable them to mount rapid and effective immune responses to novel viral infections. Such populations with natural resistance to SARS-CoV-2 infection may prove to be a valuable resource for serological factors as well as the development of vaccines and drugs for the effective prevention and therapy of COVID-19.

Competing Interests

The authors declare that they have no competing interests.

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