Research Article ISSN 2639-9458

Microbiology & Infectious Diseases

Inverse Association of COVID-19 and Malaria: Natural Immunity to SARS-CoV-2 Infection?

Randall E. Harris, MD, PhD[1], and Alexander S. Rosemurgy, MD, FACS[2]

[1]*Colleges of Medicine & Public Health, The Ohio State University Columbus, Ohio, USA.*

[2]*Digestive Health Institute, AdventHealth Tampa, Tampa, Florida, USA.*

***Correspondence:**
Randall E. Harris, MD, PhD, The Ohio State University, Colleges of Medicine & Public Health, 1841 Neil Avenue, Columbus, Ohio 43210-1351.

Received: 29 May 2020; **Accepted:** 18 July 2020

Citation: Randall E. Harris, Alexander S. Rosemurgy. Inverse Association of COVID-19 and Malaria: Natural Immunity to SARS-CoV-2 Infection?. Microbiol Infect Dis. 2020; 4(3): 1-3.

ABSTRACT

Rates of cases and deaths of COVID-19 from infection by SARS-CoV-2 show a sharp divergence in countries of Southeastern Asia where the pandemic first emerged compared to North America and Europe. The average rate of cases (83.7 per million) and the average death rate (2.24 per million) in these Asian countries through May 4, 2020, are 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, malaria rates show an inverse pattern: rates are negligible in North America and Europe and high in southeast Asia. Malaria induces interferons and neutralizing antibodies with proven impact against infection by certain viruses including the coronaviruses responsible for SARS, MERS and COVID-19. These data support the hypothesis that there may be natural immunity against COVID-19 in populations that have a longstanding history of widespread exposure to malarial infections, and such populations may prove to be a 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

Introduction

Drugs with antimalarial effects are currently under investigation for the therapy of infection by SARS-CoV-2 and resulting disease (COVID-19). Early data suggests that hydroxychloroquine (HCQ) is beneficial for patients with COVID-19 [1]. This relatively inexpensive antimalarial drug has been widely used for many decades in the geographic hot zones of malaria in Southeast Asia. Furthermore, recent clinical data suggest that cytokine storms that develop in some COVID-19 patients involve the same interferons that respond to infection by malarial plasmodia. Such cytokine storms in these patients are being treated with drugs that block interferon-mediated biosynthesis, release and immunoactivity of interleukins, e.g., the monoclonal antibody, tocilizumab, that blocks receptors for interleukin-6 [2].

It is well known that malaria induces interferons with proven impact against infection by certain viruses. Studies from multiple laboratories have also 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 [3-5]. Repeated malarial infections also induce the development of persisting antibodies that neutralize a broad profile of merozoite antigens [6], and neutralizing antibodies have recently been noted to have effects against SARS CoV-2 and other coronaviruses [7].

These preliminary laboratory and clinical findings motivated us to explore broad epidemiological patterns of COVID-19 rates in conjunction with rates of malaria for selected countries near the epicenter of the pandemic in China versus countries in North America and Europe.

Methods

We abstracted rates of tests for COVID-19 infection, rates of positive tests, and COVID-19 death 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 [8] 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. Differences in means of rates between the Asian and western countries were computed at weekly time intervals during 3/1/2020 - 5/4/2020. Rate differences were plotted over time and trends examined by linear regression analysis.

Results

The evolving cumulative numbers and rates of cases and deaths reported for COVID-19 show a sharp divergence in countries of Southeastern Asia compared to North America and Europe. As shown in the Table, the average cumulative rate of cases (83.7 per million) and the average cumulative death rate (2.24 per million) in the Asian countries through May 4, 2020, 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, P<0.001). For these same countries, the average frequency of positive tests among all tests for COVID-19 in the Asian countries (1.8%) was 82% less than the corresponding frequency (10.1%) in 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.

Of particular interest is the low rate of COVID-19 deaths in the huge population of India (population: 1.37 billion) which borders Southwestern China (population: 1.44 billion). Through May 12, 2020, the reported death rate for COVID-19 in India (1.8 per million) was 44% less than the corresponding rate for China (3.2 per million).

The table also includes recently reported incidence rates of malaria for the countries of North America and Europe versus Southeast Asia [9]. The epidemiological pattern clearly suggests that the incidence rates of malaria are inversely related to the prevalence and mortality of COVID-19, e.g., COVD-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 cumulative COVID-19 death rates for the 11 countries of Southeastern Asia versus those of North America and Europe during 4/1/2020-5/4/2020. 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 death rate for the countries of North America and Europe were more than 100-fold higher than for the countries of Southeastern Asia.

Country	COVID-19 Tests/M	COVID-19 Cases/M	COVID-19 Deaths/M	Malaria Cases Incidence/1,000
North American & European Countries				
United States	22,689	3,672	212	0
Canada	24,359	1,610	102	0
Italy	36,244	3,505	481	0
Spain	41,332	5,359	548	0
Germany	30,400	1,984	83	0
France	16,856	2,596	386	0
Portugal	44,132	2,521	105	0
Great Britain	19,026	2,807	423	0
Netherlands	13,767	2,398	302	0
Switzerland	33,092	3,467	207	0
Austria	31,742	1,738	67	0
Mean (95% CI)	28,513	2,878 (2,208-3,548)	265 (158-372)	0
Southeastern Asian Countries				
China	580	58	3	<0.1
Hong Kong	20,674	139	0.5	<0.1
South Korea	12,488	211	5	<0.1
Malaysia	6,588	197	3	0.1
Philippines	1,194	88	6	0.3
Pakistan	1,007	97	2	4.9
Thailand	3,264	43	0.8	0.8
Viet Nam	2,681	3	0.1	0.1
Cambodia	745	7	0.2	18.4
Indonesia	444	44	3	5.8
India	864	34	1	7.7
Mean (95% CI)	4,594	83.7 (39-128)	2.24 (1.0-3.5)	3.5 (0.2-6.8)
Excl. China (95% CI)	4,995	86.3 (37-135)	2.16 (0.8-3.5)	3.8 (0.2-7.4)

Table 1: Cumulative COVID-19 rates compared to the incidence of malaria in countries of Southeastern Asia, North America and Europe, 12/01/2020 – 5/4/2020.

Tests per million in China were estimated assuming the positivity rate among tests was 0.1.

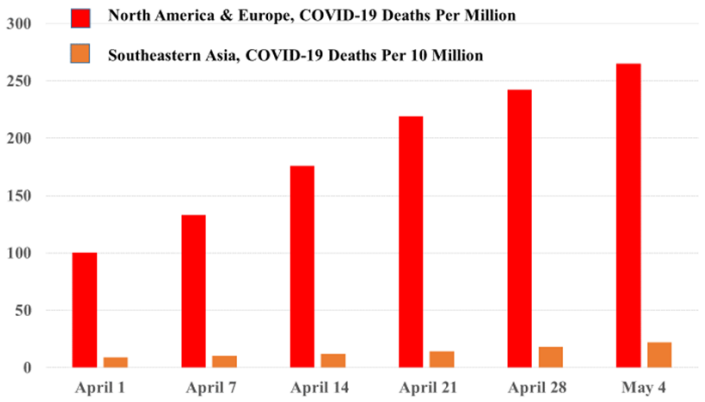

Figure 1: Cumulative COVID-19 death rates in countries of Southeastern Asia versus North America and Europe, 4/1/2020-5/4/2020.

Discussion

While it can be argued that the inverse association of COVID-19 and malaria infections may primarily reflect disparities in demographics, testing, reporting, and infection control, the potential for biological effects must not be ignored. The epidemiological data characterizing the current COVID-19 pandemic combined with the international pattern of malaria 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 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 resource for serological factors as well as the development of vaccines and drugs for the effective prevention and therapy of COVID-19.

References

1. Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents. 2020; 105949.
2. Mehta P, McAuly DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. The Lancet. 2020; 395: 1033-1034.
3. King T, Lamb T. Interferon-γ: the Jekyll and Hyde of malaria. PLoS Pathog. 2015; 11: e1005118.
4. Strayer DR, Dickey R, Carter WA. Sensitivity of SARS/MERS CoV to interferons and other drugs based on achievable serum concentrations in humans. Infect Disord Drug Targets. 2014; 14: 37-43.
5. Fauci AS, Lane HC, Redfield RR. Covid-19-navigating the uncharted. N Engl J Med. 2020; 382: 1268-1269.
6. Jiang S, Hillyer C, Du L. Neutralizing antibodies against SARS-CoV-2 and other human coronaviruses. Trends in Immunology. 2020; 41: 355-359.
7. Corti D, Lanzavecchia A. Broadly neutralizing antiviral antibodies. Annu Rev Immunol. 2013; 31: 705-742.
8. https://www.worldometers.info/coronavirus/
9. https://ourworldindata.org/malaria