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Review Article

COVID-19 Virus Infection and Transmission are Observably Less in Highly Dengue-Endemic Countries: Is Pre-Exposure to Dengue Virus Protective Against COVID-19 Severity and Mortality? Will the Reverse Scenario Be True?

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ABSTRACT

Global severity maps of ongoing dengue epidemic and COVID-19 pandemic do not tend to overlap. Countries with high dengue endemicity (>1.5 million cases/year) are observably less hit by COVID-19 in terms of infection, transmission and mortality. Based on non-overlap of dengue and COVID-19 severity maps in general and increasing evidences of SARS-CoV-2 false-positivity in dengue antibody tests, we wonder whether regular pre-exposure to dengue virus (DENV) in highly dengue endemic countries is providing some extent of protection against COVID-19 severity. We also wondered whether immunization of susceptible populations in dengue non-endemic countries (e.g. Europe and North America) with available live-attenuated dengue vaccines, will cue the anti-viral immune response to thwart COVID-19. Risk of developing post-vaccination antibody-dependent enhancement (ADE) is low as dengue is not endemic in the aforesaid regions. Understanding the consequences of dengue and COVID-19 co-endemicity in the upcoming days is another area of huge concern. Although, it appears that dengue-induced immunity is 'thwarting' COVID-19, it is not clear whether conversely, COVID-19 convalescent individuals will also be resistant to future dengue attacks. On the contrary, such individuals may show higher susceptibility to DENV due to ADE caused by cross-reactive COVID-19 antibodies. The latter may bind to DENV without neutralizing the virus; instead, such antibodies may facilitate cellular entry of DENV by means of their Fc-regions attached to the susceptible cells. This possibility also cautions against complications that may arise on implementing SARS-CoV-2 vaccinations in highly dengue endemic countries.

Introduction

Dengue is caused by an arbovirus i.e. the dengue virus (DENV) (Genus: Flavivirus, Family: Flaviviridae). DENV is medically the most important arthropod-borne virus prevalent globally. Currently, DENV is endemic to most of the tropical and sub-tropical regions of the world where its vector, the Aedes mosquitoes are prevalent. At present, an estimated 396 million, i.e. almost 0.4 billion people are infected with DENV in Latin America, Southeast Asia, Africa and Indian subcontinent. Almost 96 million infections occur every year with roughly 80% being asymptomatic. The remaining cases manifest with morbidity of different degrees ranging from dengue fever to more severe forms like dengue haemorrhagic fever and dengue shock syndrome. DENV infection causes about 25,000 deaths annually in about 128 countries across the globe [1, 2].

The human race is currently going through the scourge of COVID-19 pandemic, caused by the SARS-CoV-2 (Subgenus: Sarbecovirus; Family: Coronaviridae) which originated from Wuhan, China last December (2019) [3]. As on 11th June 2020, the total number of infected people was over 7.4 million with a death toll of about 0.42 million worldwide. The virus is highly transmissible from human to human and

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played havoc in Europe, United States and the Middle East after causing severe epidemic in China. Currently, the infections are on the rise in India and certain Latin American countries like Brazil and Mexico.

COVID-19 and Dengue Global Severity Maps Do Not Tend to Overlap

While looking at the epidemiology and global spread of COVID-19, it appeared that COVID-19, in general, is infecting a smaller number of people and showing lower transmission rate in high DENV-endemic regions (>1.5 million cases/year) such as the Latin America, Africa, SE Asia and the Indian subcontinent during late March and early April, 2020. For instance, India and many countries in Latin America (like Mexico and Brazil) recorded much fewer cases with insignificant mortalities compared to China, Italy, Spain, France, UK and USA, despite higher population density, lower average longevity and relatively poor healthcare systems (Tables 1A & 1B). During a week's gap in March-April, the high DENV-endemic regions recorded an increase from 5 to 12 SARS-CoV-2 infections/million populations while the low endemic sporadic DENV prevalent countries recorded a rise from 200 to 400 infections/million population (Tables 1A & 1B).

Table 1A: COVID-19 infections and mortality (as of 28th March, 2020) in a representative list of high dengue endemic and not-so-endemic countries of the globe [17].

	COVID-19 cases in high dengue endemic countries			**COVID-19 cases in countries where dengue is less endemic/sporadic**			
Country	***Population (in million)*** [13]	***Confirmed cases***	***Deaths***	***Country***	***Population (in million)*** [18]	***Confirmed cases***	***Deaths***
India	1366	887	20	China	1433	81,394	3,295
Bangladesh	163	48	5	Italy	60	86,498	9,134
Singapore	5	732	2	Spain	47	65,719	5,138
Malaysia	32	2,161	26	Germany	84	50,817	351
Japan	127	1,499	49	France	65	32,964	1,995
Mexico	128	717	12	Iran	83	32,332	2378
Brazil	211	3,477	93	UK	68	14,543	759
Argentina	45	690	17	USA	329	1,04,205	1701
Sudan	42	5	1	Australia	25	3,573	14
TOTAL	**2119**	**10,216**	**225**	**TOTAL**	**2194**	**4,72, 045**	**24,765**

Table 1B: COVID-19 infections and mortality (as of 4th April, 2020) in a representative list of high dengue endemic and not-so-endemic countries of the globe [17].

	COVID-19 cases in high dengue endemic countries			**COVID-19 cases in countries where dengue is less endemic/sporadic**			
Country	***Population (in million)*** [13]	***Confirmed cases***	***Deaths***	***Country***	***Population (in million)*** [18]	***Confirmed cases***	***Deaths***
India	1366	3,588	99	China	1433	81,669	3,329
Bangladesh	163	88	9	Italy	60	1,24,632	15,362
Singapore	5	1,189	6	Spain	47	1,26,168	11,947
Malaysia	32	3,662	61	Germany	84	96,092	1,444
Japan	127	3,139	77	France	65	89,953	7,560
Mexico	128	1,890	79	Iran	83	55,743	3,452
Brazil	211	10,360	445*	UK	68	41,903	4,313
Argentina	45	1,451	43	USA	329	3,11,637	8,454
Sudan	42	10	2	Australia	25	5,687	34
TOTAL	**2119**	**25,377**	**821**	**TOTAL**	**2194**	**9,33,484**	**55,895**

Mortality was 2-3% of the infections in DENV-endemic versus 5-6% in low DENV reporting countries (Tables 1A & 1B). Strikingly, the COVID-19 mortality in high DENV endemic countries was 0.1-0.4 per million populations compared to 11-25 in the DENV non-endemic regions, over a week's time (28th March to 4th April 2020). As of 3rd June 2020, about two months later, mortality increased to 24 per million populations (5% of infections) in highly dengue endemic countries against 118 COVID deaths/million populations (8% of infections) in the non-dengue parts of the world as per our estimates (Table 1C). The rise in mortality is mostly contributed by Brazil and Mexico, where SARS-CoV-2 is spreading like wildfire in recent times. On comparison of the global severity maps of COVID-19 and DENV, it is clear that countries

worst hit by COVID-19 are not highly endemic for dengue with the exceptions of Brazil and Mexico [2, 4]. In the aforesaid map for COVID-19, the countries under severe COVID-19 attack, surprisingly do not tend to overlap with the areas in the DENV global map, which record more than 1.5 million DENV infections per year [2].

Table 1C: COVID-19 infections and mortality (as of 3rd June, 2020) in a representative list of high dengue endemic and not-so-endemic countries of the globe [17].

	COVID-19 cases in high dengue endemic countries			**COVID-19 cases in countries where dengue is less endemic/sporadic**			
Country	***Population (in million)*** [13]	***Confirmed cases***	***Deaths***	***Country***	***Population (in million)*** [18]	***Confirmed cases***	***Deaths***
India	1366	2,16,427	6,087	China	1433	83,021	4,634
Bangladesh	163	55,140	746	Italy	60	2,33,836	33,601
Singapore	5	36,405	24	Spain	47	2,87,012	27,127
Malaysia	32	7,970	115	Germany	84	1,84,214	8,680
Japan	127	16,930	894	France	65	1,51,325	28,940
Mexico	128	97,326	10,637	Iran	83	1,60,696	8,012
Brazil	211	5,60,737	31,417	UK	68	2,79,856	39,728
Argentina	45	18,319	570	USA	329	18,88,150	1,08,354
Sudan	42	5310	307	Australia	25	7,229	102
TOTAL	**2119**	**10,14,564**	**50,797**	**TOTAL**	**2194**	**32,75,339**	**2,59,178**

Current Understanding on Effect of Weather and Climate on COVID-19

One may argue that the high DENV endemic regions are relatively warmer than the regions worst affected by COVID-19 pandemic, but from overall consensus from past and current data, it appears that SARS-CoV-2 can be transmitted in hot and humid weather as well [5, 6].

Childhood BCG Vaccination and COVID-19

Countries where BCG vaccination is recommended (in early childhood) have been also observed to be less affected by COVID-19 [7, 8]. This appears true for highly DENV endemic (& BCG vaccine compliant) countries like India and Argentina but in question for low/sporadic DENV-reporting (yet BCG vaccination compliant) countries like Iran and China, where COVID-19 had serious impact so far. The high levels of infections and mortality in Brazil (another BCG vaccination compliant country) has also put the theory that BCG vaccination could be protective against COVID-19, into question (Table 1C).

Pre-Exposure to Dengue Protects Against COVID-19?

From the above observations, it is highly probable that pre-exposure to DENV might provide some degree of cross-protection to SARS-CoV-2 infection, rendering it less severe in the regions where DENV infections occur rampantly and regularly. Our proposition is supported by one report from Singapore in Lancet Infectious Diseases, where an elderly man and a woman (both 57 years) were originally COVID-19 virus-positive but found false-positive in serological tests for dengue, including DENV-IgM and IgG [9]. Both patients were confirmed DENV RNA-negative by qRT-PCR. So, it is probable that SARS-CoV-2 shares antigenic similarity with DENV and elicits antibodies that are detected by DENV-serological tests. These tests use DENV antigens (usually DENV envelope) to capture anti-DENV IgM or IgG in the patients' sera.

One possible explanation of this phenomenon is that due to antigenic similarity, SARS-CoV-2 may trigger production of anti-DENV antibodies from immunological memory (memory T and B cells) to previous DENV exposure, which the patient may be unaware of (asymptomatic). The other possibility is that antibodies to SARS-CoV-2 cross react with DENV antigens used in DENV serological tests. Furthermore, the original seropositive sample as well as additional urine and blood samples from the aforesaid male patient were also found negative for DENV, chikungunya, and zika viruses by RT-PCR. The above report is no longer anecdotal as similar observations are now being reported from other countries as well like India [10, 11].

We are of opinion that pre-existing immunological memory to DENV exposure, in the form of DENV antibodies and memory B and T cells, may have a negative impact on transmission, severity and pathogenesis of COVID-19 infections. Regular exposure to DENV (germ theory) is also likely to cue the innate immunity in people in the highly dengue endemic regions towards ready response to exotic viral infections like SARS-CoV-2. So, prior DENV-exposure may be one of the reasons why DENV endemic countries like Japan, Singapore and South Korea could flatten the curve of COVID-19 cumulative rise of infections (i.e. curtailed transmission rate dramatically) over time more effectively than the countries where DENV is not highly endemic. For instance, India contributing 34 of 96 million annual global DENV infections recorded about 0.3 million COVID-19 positive cases as on 11th June 2020 with overall mortality of only 8107 patients, compared to over 1 million and 40,000 deaths in USA and UK respectively [1, 2].

Possible Reasons behind Why Brazil is Hit Hard by COVID-19 Pandemic?

Brazil has not observed preventive measures to check the spread of COVID-19 like social distancing, quarantine and lockdown in the early phases of the pandemic. Super-spreaders (high virus titre in nasopharynx, throat and sputum) have been already recorded for SARS-CoV-2 [12]. Increased rate of transmission due to lack of precautionary measures (especially social distancing) and consequent exposure to high virus loads, especially among the young adult and middle-aged population (i.e. below 60 years) are important factors that can overwhelm the cross-protective effects induced by DENV pre-exposure. From the scenario in Brazil, it appears that mild to moderate exposure to SARS-CoV-2 is triggering the immune system to produce anti-dengue virus antibodies (memory B and T cells) which provide some degree of cross-protection against SARS-CoV-2 replication in the affected individuals (possibly due to antigenic similarities between the two viruses). So, India is showing less mortality as infection is spreading but observance of lockdown and personal protective measures have caused the virus to spread slowly and in low to moderate titres among susceptible people.

However, if infection is heavy in the first instance due to lack of social distancing and personal protective measures, as in Brazil, exposure to too much virus due to close contacts and consequent high virus replication in the infected individuals will result in increased disease severity "faster" than the gradual production of anti-dengue antibodies and initiation of their protective effects. It is well known that in most viral diseases, exposure to higher virus inoculum/titre goes hand in hand with progressive increase in disease manifestation and severity. Overall, exposures to huge number of SARS-CoV-2 result in initiation of cytokine storm, massive damage to lungs, multi-organ failure, blood clotting etc., culminating in higher mortality which could not be 'timely' controlled by anti-dengue immunity [13].

The Dengue-COVID Conflict: Possible Outcomes of SARS-CoV-2 Vaccination in Highly Dengue Endemic Regions

Sera from COVID-19 recovered patients have been found to cross-react with DENV antigen culminating in false-positive results in dengue IgM and IgG antibody tests [9-11]. This has serious implications for countries where dengue and COVID-19 are co-existent at large like India, Brazil and Mexico. Monitoring seroprevalence will be difficult for both diseases due to this cross-reactivity. Antibodies elicited by COVID-19 may have two outcomes in highly dengue endemic countries: A) either they will reduce dengue virus infections by binding to DENV and thereby blocking infection of cells or B) they may augment DENV infection if COVID-19 induced antibodies do not neutralize the infecting virus and cause ADE.

Based on facts presented so far, vaccination against SARS-CoV-2 targeting the spike protein in highly dengue endemic parts of the world will elicit anti-SARS-CoV-2 antibodies in the vaccinated population which may have the following unforeseen consequences. Such antibodies may aggravate future DENV infections as explained above; render serosurveillance for dengue complicated due to cross-reactivity and giving false-positive results in dengue serological tests; and more importantly render secondary subsequent waves of COVID-19 outbreaks more dangerous. This will happen if such outbreaks are caused by mutated SARS-CoV-2 strains with altered spike protein [14]. In that case, antibodies to one strain of SARS-CoV-2 may not neutralize a subsequent emergent strain, instead, they will bind to the virus particles and cause 'enhanced' infection of the cells (ADE) [15].

Dengue Vaccines May Be Effective Against COVID-19 Spread in Dengue Non-Endemic Regions?

In the forefront of ongoing battle against COVID-19 pandemic, we are desperately in look out for vaccines and antivirals. Based on the evidence that SARS-CoV-2 has antigenic similarity to DENV and elicits antibodies that are detected by DENV serological tests, we wonder whether immunization of susceptible population at risk (e.g. people in the United States and Europe at present) with live attenuated dengue vaccines (e.g. CYD-TDV or DENVax/ Tak-003) will cue the anti-viral immune response to bring down (even partially protect against) SARS-CoV-2 replication and severity [9-11, 16].

The risk of developing post-vaccination antibody-dependent enhancement (ADE) in subsequent exposure to DENV is low as dengue is not endemic in the countries, where COVID-19 is currently rampant and spreading like bushfire. If our observations reach the scientific community who have the opportunity to handle COVID-19 in high containment laboratory facilities, they can quickly check if there is cross-reactivity between dengue fever convalescent sera and SARS-CoV-2. There are also animal models for SARS-CoV, and it should be straightforward to determine whether available dengue vaccines offer any protection against COVID-19. Until well-tested specific vaccines are available against SARS-CoV-2, we think available live dengue vaccines may be tested quickly and if there is any promise, implemented immediately to immunize the populations currently at highest risk of COVID-19 attack in regions of Europe, North America and temperate Asia (China, Iran), where dengue is either sporadic or not highly endemic.

Conclusion

There appears to be a stark contrast in COVID-19 spread and severity between countries in the tropical and sub-tropical regions and those in the temperate regions. In general, China, Western Europe, and USA showed more vulnerability to COVID-19 compared to some of the less developed parts of the world like the Indian subcontinent, South-East Asia, Latin America and Africa. But current understandings suggest that temperature and climate do not appear to significantly influence the transmission and survival of SARS-CoV-2 in the environment. The aforesaid tropical and sub-tropical countries record DENV epidemics on a regular basis. Therefore, it appears that populations exposed to regular dengue virus epidemics are relatively resistant to COVID-19 transmission and pathogenesis.

Incidentally, many of the highly dengue endemic countries also overlap with those where universal BCG vaccination is recommended at early childhood against tuberculosis. So, it is also thought that BCG vaccination may have a protective role against COVID-19. This may be true as BCG vaccination boosts cell mediated immunity and likely to

augment innate immune response. But one may also observe several important exceptions such as China and Iran. BCG vaccination is still carried out in these countries, but they were heavily affected by COVID-19 in terms of transmission, severity and mortality. Interestingly, DENV incidences are low/sporadic in these two countries, supporting our proposition.

Given the cross-reactivity between SARS-CoV-2 and DENV, serosurveillance for these viruses must be carried out carefully in regions where both these viruses are co-existent now. Pros and cons of vaccination strategies against SARS-CoV-2 have to be evaluated scrupulously before implementing them in DENV-endemic countries of the world.

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Conflicts of Interest

None.

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