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Review Article

COVID-19 infection and transmission are observably less in highly Dengue-endemic countries

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Abstract

We observed that global severity maps of ongoing dengue epidemic and COVID-19 pandemic do not overlap. Countries where dengue is highly endemic (>1.5 million cases/year) appear to be less hit by COVID-19 pandemic in terms of infection and transmission. Other evidences also support our proposition that pre-exposure to other wide-spread viral infections like dengue may thwart the spread of the COVID-19 pandemic.

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Introduction

Dengue is caused by an arbovirus i.e. the dengue virus (DENV) (genus: *Flavivirus,* Family: *Flaviviridae*). DENV virus 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 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 25000 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 28th March, 2020, the total number of infected people was almost 6 lakhs with a death toll of more than 27,000 worldwide. The virus is highly transmissible from human to human and is currently playing havoc in Europe, Middle-East, Australia and the United States after causing severe epidemic in China.

COVID-19 and dengue global severity maps *do not overlap*

While looking at the epidemiology and global spread of COVID-19, it appeared that COVID-19 is infecting a smaller number of people and showing lower transmission rate in high DENV-endemic countries (>1.5 million cases/year) such as the Latin America, Africa and the Indian subcontinent. For instance, India, Brazil and Argentina are recording much fewer cases with insignificant mortalities compared to China, Italy, Spain, France, UK and USA,

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despite higher population density, lower average longevity and relatively poor healthcare systems (**Table 1**). The high DENV-endemic regions recorded about 5 SARS-CoV-2 infections per million population while the low endemic/sporadic DENV prevalent countries recorded approximately 200 infections/million population. Mortality is 2% of the infections in DENV-endemic versus 5% in low DENV reporting countries (**Table 1**).

On comparison of the global severity maps of COVID-19,[4] and DENV,[2] it is clearly evident that countries worst hit by COVID-19 are not highly endemic for dengue. In the aforesaid map for COVID-19, the countries currently under severe COVID-19 attack, surprisingly, ***do not overlap*** with the red or deep orange areas in the DENV global map,[2] which record more than 1.5 million DENV infections per year.

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]

Pre-exposure to Dengue protects against COVID-19?

From the above observations, it is highly probable that DENV sero-conversion in people in DENV endemic countries might provide cross-protection to SARS-CoV-2 infection, rendering it less severe in the regions where DENV infections occur rampantly.

Our proposition is supported by a recent publication from Singapore in *Lancet Infectious Diseases*,[7] 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

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and/or IgG. Both patients were confirmed DENV RNA-negative by qRT-PCR. *So, it is probable that SARS-CoV-2 shares antigenic similarity with DENV and may cross-react with DENV-specific antibodies used in the DENV serological tests*. Furthermore, the original sero-positive 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.

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 is also likely to cue the innate immunity in people in the highly endemic regions towards ready response to other exotic viral infections (*viral interference*).

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[8] recorded only 887 COVID-19 positive cases so far (at the time of writing) with overall mortality of 20 cases.

Dengue anti-sera and dengue vaccines may be effective against COVID-19 spread?

If DENV sero-positivity acts against COVID-19 spread and severity, convalescent human sera with proven high DENV-IgG titres may be useful in treating severe COVID-19 cases in the non-DENV endemic parts of the world, where the COVID-19 pandemic has hit hard.

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Based on the anecdotal evidence that SARS-CoV-2 may cross react with DENV antibodies,[7] another vital question is whether immunization of *susceptible population/population at risk* (eg. people in the United States at present) with *live attenuated* dengue vaccines (eg. CYD-TDV or DENVax/ Tak-003)[9] will cue the anti-viral immune response to bring down SARS-CoV-2 replication and severity? 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.

Childhood BCG vaccination and COVID-19

Countries where BCG vaccination is recommended (in early childhood)[10] have been also observed to be less affected by COVID-19.[11] This appears true for highly DENV endemic (& BCG vaccine compliant) countries like India, Brazil 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 (**Table 1**).

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.

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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 antiviral 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.

However, all the above observations and speculations are from anecdotal evidences and historical perspectives and presently at hypothesis levels. They need rigorous validation by proper experiments and epidemiological studies.

Conflict of interest: Nothing to declare.

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Table 1. 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[12]

	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)***[13]	***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**

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Supplementary Figure 1*. Global distribution of dengue (top panel) and COVID-19 (bottom panel).

The global map in the top panel was accessed from published article[2] while that in the bottom panel was accessed from the Internet (https://www.cnbc.com/2020/03/26/worldwide-coronavirus-cases-top-500000-doubling-in-just-over-a-week.html accessed on 28th March, 2020).

*Not for publication but to help with the review process.

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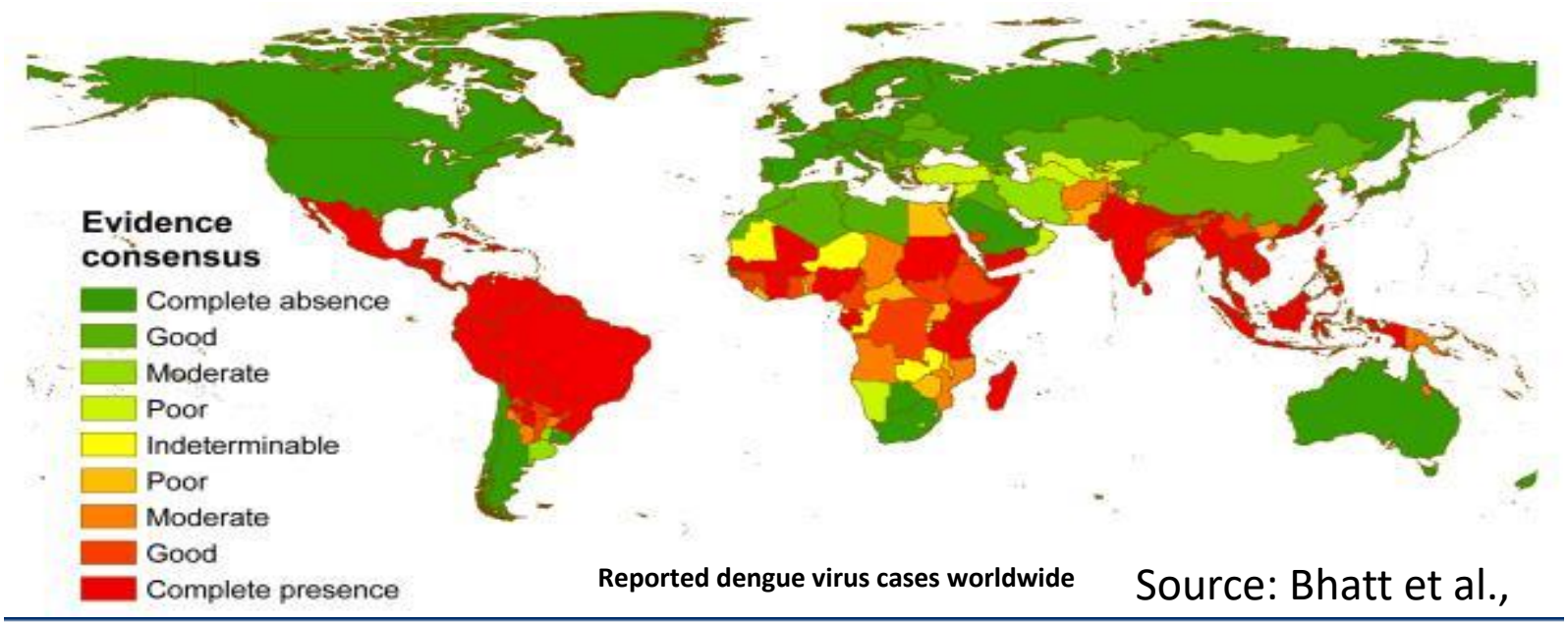
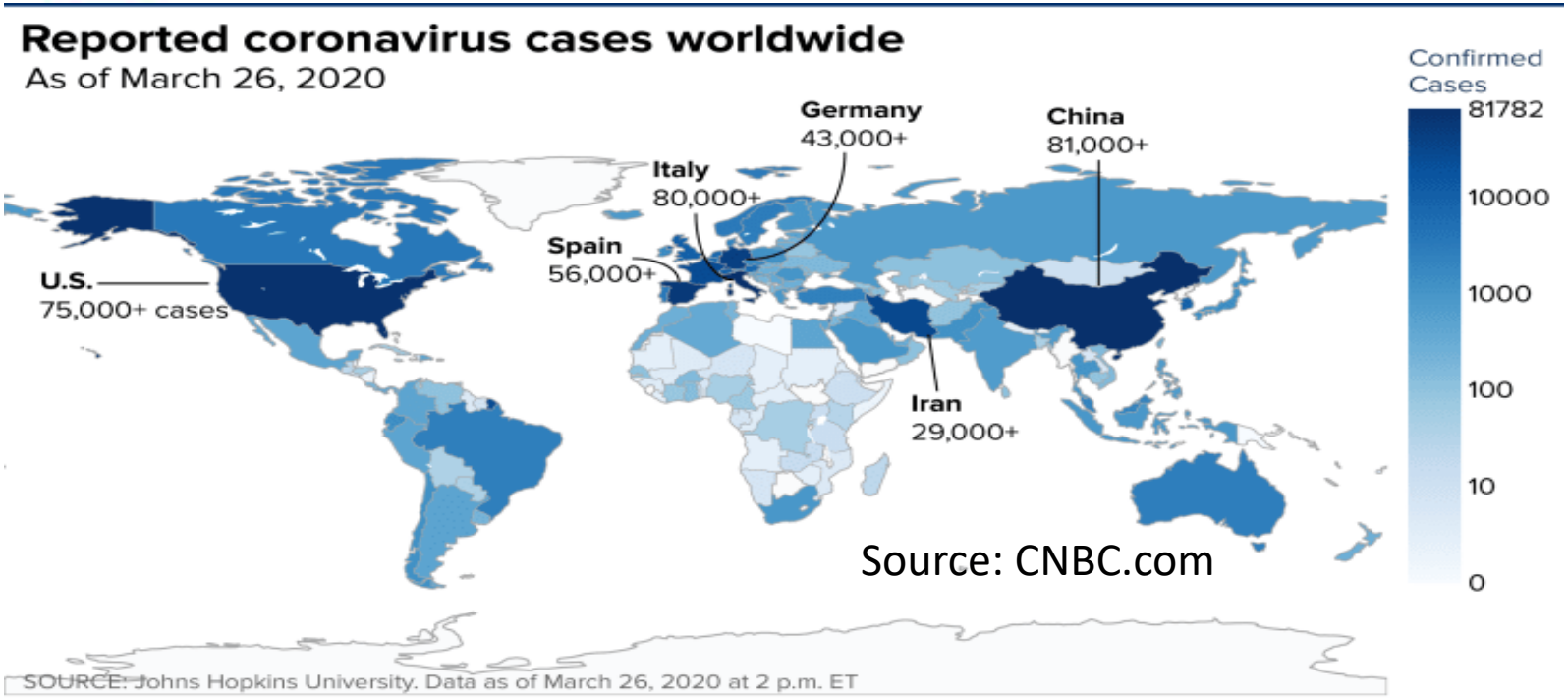
Figure 1.



Reported dengue virus cases worldwide Source: Bhatt et al.,



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