

*Review Article v3*

## **COVID-19 virus infection and transmission are observably less in highly Dengue-endemic countries: Can Dengue vaccines be “repurposed” to prevent COVID-19?**

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## Abstract

Global severity maps of ongoing dengue epidemic and COVID-19 pandemic do not 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 and evidence of SARS-CoV-2 serological cross-reactions with dengue, we wonder whether immediate immunization of susceptible populations in Europe, North America and Asia (China, Iran) with available live-attenuated dengue vaccines, will cue the anti-viral immune response to thwart COVID-19 (viral interference). Risk of developing post-vaccination “*Antibody-dependent Enhancement*” is low as dengue is not endemic in the aforesaid regions.

## 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 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.<sup>1, 2</sup>

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).<sup>3</sup> As on 14<sup>th</sup> April, 2020, the total number of infected people was over 19 lakhs with a death toll of about 1.2 lakhs worldwide. The virus is highly transmissible from human to human and is currently playing havoc in Europe, United States, Middle-East and Australia 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 many countries in Latin America (like Mexico) are recording 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 (**Table 1**). The high DENV-endemic regions recorded an increase from 5 to 12 SARS-CoV-2 infections per million population while the low endemic/sporadic DENV prevalent countries recorded a rise from 200 to 400 infections/million population over a week (**Table 1**).

Mortality is 2-3% of the infections in DENV-endemic versus 5-6% in low DENV reporting countries (**Table 1**). Strikingly, the COVID-19 mortality in high DENV endemic countries is 0.1-0.4 per million population compared to 11-25 in the DENV non-endemic regions, over a week's time (28<sup>th</sup> March to 4<sup>th</sup> April, 2020)

On comparison of the global severity maps of COVID-19,<sup>4</sup> and DENV,<sup>2</sup> 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,<sup>2</sup> 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.<sup>5,6</sup>

## Pre-exposure to Dengue protects against COVID-19?

From the above observations, it is highly probable that pre-exposure to DENV might provide 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 a recent publication from Singapore in *Lancet Infectious Diseases*,<sup>7</sup> 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/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 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. The other possibility is that antibodies to SARS-CoV-2 cross react with DENV antigen(s) used in 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 (*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 (*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<sup>8</sup> recorded only 3,588 COVID-19 positive cases as on 4<sup>th</sup> April, 2020 with overall mortality of 99 patients.

### **Dengue vaccines may be effective against COVID-19 spread?**

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,<sup>7</sup> we wonder whether immunization of *susceptible population/population at risk* (eg. people in the United States and Europe at present) with *live attenuated* dengue vaccines (eg. CYD-TDV or DENVax/ Tak-003)<sup>9</sup> will cue the anti-viral immune response to bring down (even partially protect against) 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.

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-CoVs 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.

### **Childhood BCG vaccination and COVID-19**

Countries where BCG vaccination is recommended (in early childhood)<sup>10</sup> have been also observed to be less affected by COVID-19.<sup>11</sup> 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.

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.

However, all the above speculations are from preliminary observations and evidences 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 1A. COVID-19 infections and mortality (as of 28<sup>th</sup> March, 2020) in a representative list of high dengue endemic and not-so-endemic countries of the globe<sup>12</sup>

COVID-19 cases in high dengue endemic countries				COVID-19 cases in countries where dengue is less endemic/sporadic			
Country	Population (in million) <sup>13</sup>	Confirmed cases	Deaths	Country	Population (in million) <sup>13</sup>	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 4<sup>th</sup> April, 2020) in a representative list of high dengue endemic and not-so-endemic countries of the globe<sup>12</sup>**

COVID-19 cases in high dengue endemic countries				COVID-19 cases in countries where dengue is less endemic/sporadic			
Country	Population (in million) <sup>13</sup>	Confirmed cases	Deaths	Country	Population (in million) <sup>13</sup>	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
<b>TOTAL</b>	<b>2119</b>	<b>25,377</b>	<b>821</b>	<b>TOTAL</b>	<b>2194</b>	<b>9,33,484</b>	<b>55,895</b>

\* Brazil, a highly DENV-endemic country recorded >10000 infections and >400 deaths. But we also have to consider that Brazil has not observed social distancing and quarantine during the above period. Super-spreaders (high virus titre in nasopharynx, throat and sputum) have been already recorded<sup>14</sup> for SARS-CoV-2 and increased rate of transmission (due to lack of precautionary measures like social distancing and lockdown) can overwhelm cross-protection effects induced by DENV pre-exposure.

**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<sup>2</sup> 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.

Figure 1.



