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Considerations on Cross Effects between Dengue Serotypes and Possible Implications for the Future of Covid 19 Pandemic

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ABSTRACT

Abbreviations: DF: Dengue Fever; DHF: Dengue Hemorrhagic Fever; DSS: Dengue Shock Syndrome; ADE: Antibody-Dependent Enhancement; VADE: Vaccine Induced Antibody-Dependent Enhancement; WHO: World Health Organization

Opinion

Viruses responsible for Dengue as well as those responsible for COVID are both positive-strand RNA viruses (+ssRNA viruses), but dengue is due to a flavivirus while Covid is due to a coronavirus. Moreover, dengue is an arboviral disease (transmitted by several *Aedes sp.* principally *A. aegypti*), while COVID as well as most other coronaviral diseases such as SARS 1 and common cold are transmitted by airborne droplets and to a lesser extent by contaminated surfaces. There are well known studies on positive and negative cross effects of different Dengue serotypes, and much less is known in the case of COVID: here we point a possible outcome of further evolution of COVID, leading to potentially dangerous cross effects. It has been shown that a zero-dimensional approach of dengue epidemics is not adapted, and that spatialisation is essential [1,2]. In fact, one is led to use a hierarchical approach: the range of infected mosquito flight is limited to the immediate neighbourhood, and longer range propagation is due to movements of infected humans to the village centre or to farther destinations where the vector is already present, hence a way to further dissemination. The fact that coronavirus diseases are not arthropod borne leads to a very different (and in a sense simpler) two dimensional modelling. There are four serotypes of dengue virus (a fifth is suspected: [3]): all belong to the family Flaviviridae; genus Flavivirus.

All can infect humans with either an asymptomatic form or a common Dengue Fever (DF), Dengue Hemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS). From the huge but easily available literature it emerges a quasi-consensus that the latter two, DHF and DSS, are more likely in the case of a secondary infection than with a primary one. Although there are some claims that the same patient can be infected twice by the same serotype, it is generally accepted that in most cases an episode with a given serotype gives long term protection against this one, and short term protection ranging from a few months up to two years against the others, but no long term

protection against a secondary infection by a different serotype: on the opposite, it can lead to more severe forms as mentioned above. The kinetics of IgM and IgG are far too rapid to explain that. The aggravated symptoms in the case of a delayed secondary infection by a different serotype is usually called Antibody-Dependent Enhancement (ADE). Studies in locations where several serotypes have appeared (e.g. Bangkok, Cuba, New Dehli, and the Texas-Mexican border) tend to show that the relative frequency of DHF and DSS (that is the ratio of severe cases to the number of asymptomatic or ordinary dengue fever) is higher in places where the interval of appearance of different serotypes is longer.

It is also interesting to study the still ongoing Dengvaxia dengue vaccine controversy about Vaccine Induced Antibody-Dependent Enhancement (VADE). If one looks at the evolutionary genetics of dengue virus [4], one sees that it can be traced for at least one thousand years from sylvatic forms, and that the first split was that of Dengue 4, followed by a split of Dengue 2, while Dengue 1 and 3 split more recently, slightly more than two hundred years ago. There is a rather large genetic divergence between the different serotypes, and also a strong antigenic distance [5]. Nevertheless, the four serotypes are responsible for essentially the same disease with essentially the same symptoms, and only sequencing can identify the serotype involved in a given outburst. As mentioned above, protection is durable against a re-infection by the same serotype, but only briefly protecting, then adversely effective against an infection by another serotype. The similarity of the symptoms compared to the genetic distance of the serotypes is striking. The history of coronavirus serotypes in humans is quite different [6]: indeed there are four different branches of coronavirus ranging from "Alpha" to "Delta", and there are two benign HCoVs (human affecting) in the branch "Alpha", while the five other human coronavirus all belong to the branch "Beta": two benign in Beta-Cov Lineage A, MERS-CoV in Beta-Cov Lineage C, while SARS-CoV1 and SARS-CoV2 (COVID 19) both belong to Beta-Cov Lineage B.

HCoV-NL63 and HCoV-229E emerged respectively about 600 and 200 years ago, HCoV-OC43 and HCoV-HKU1 about 120 and 70 years ago (although HCoV-NL63 and HCoV-HKU1 are ancient, both were identified only in 2004) , while SARS-CoV 1 emerged in 2002, MERS-CoV in 2006 and SARS CoV 2 (COVID 19) in 2019. There are many controversies on possible cross effects between the different HCoVs, none really convincing, either as protective or pejorative. We will only consider possible cross-effects between SARS-CoV2 serotypes. This has been already envisaged (e.g. [7] and [8]) but very shortly after the onset of the pandemic. As we have seen, the history of Dengue is much older than that of Covid. Nevertheless, in less than two years, a large number of SARS CO-2 variants appeared, with different transmission rates and virulences. Also, the fact that previous contamination did not protect completely from other variants was rather unexpected. It seems that in the case of Omicron, re-infection by the same variant (and even the same sub-variant) is commonly observed. Luckily, previous infections, as well as vaccination, seem to drastically reduce the number of serious cases. As for now, the genetic distance between the variants is obvious but nevertheless much smaller than between the four Dengue serotypes, which is not surprising because of the short history of SARS-CoV2.

On the other hand, the large range of different symptoms due to different variants is remarkable, to the point that a diagnostic can sometimes be made before serotype analysis. When thinking of the future of the pandemic, the World Health Organization (WHO) points out there are three main possible outcomes:

1. "In the best-case scenario, we may see less severe variants emerge, and boosters or new formulations of vaccines won't be necessary"
2. "The virus continues to evolve, but the severity of the disease it causes reduces over time as immunity increases due to vaccination and infection"
3. "In the worst-case scenario, more highly transmissible variants may emerge".

There is a fourth possibility, which is the reason of this short communication: it is likely that the pandemic will be kept under control, and that it will evolve towards an endemic situation similar to that of the common (nevertheless often deadly) flu. But there exists a very high probability that new variants will evolve and acquire increased genetic distance from the initial serotypes in a given location, even if they do not have a high virulence or transmissibility. Because of a global immunisation against the SARS CoV2, this new variant is likely to persist locally at a low level (while a dengue local epidemic could more easily affect a distant location), but if a further mutation increases its transmissibility, it could quickly spread out. In this case, an immune system trained on distant variants or vaccines could have an inappropriate reaction leading e.g. to severe cytokine storm. Therefore, it is of course essential to maintain the vaccination effort as strongly as possible, to try to cover all countries presently under vaccinated, and to adapt vaccines to new variants, but it is also essential to keep an extreme vigilance towards unexpected strong reactions of the immune system in new outbreaks, leading to new and frequent occurences of hypercytokinemia (cytokine storm syndrome).

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Foreword

This is not as such a research paper, but as the title implies some thoughts and suggestions on the future of the SARS 2 pandemic. Bibliography will voluntarily be quite succinct, and no explicit model is presented here.

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