## If you could invent a new drug, what would it be and why?

Dengue virus is the most prevalent human arbovirus (Madewell, 2020), and yet dengue fever still rightly deserves the title of a 'neglected tropical disease'. Despite the estimated 390 million dengue infections per year with over 20% of which resulting in a severe manifestation of the disease (Bhatt *et al.*, 2013), there are currently no drugs to cure dengue fever that have left trials. This is because the virus is mainly prevalent in tropical and subtropical countries, which are primarily developing countries, that do not have the resources and budget to develop and produce such drugs. However, methods of prevention (such as the Dengvaxia vaccine) have limited efficacy and are not economically sustainable, suggesting that an antiviral drug may be the optimum way to handle this disease. Furthermore, the cost of treatment and then the loss of productivity also adds to the economic burden that affected countries suffer from, limiting future economic progression. Not only does the lack of a drug to treat dengue fever severely impact over 110 countries (Zheng *et al.,* 2021), but a similar fate also awaits multitudes of other countries as climate change expands the habitable regions of the *Aedes aegypti.* Ultimately, a drug to treat dengue fever would not only comply with the UN's sustainable development goals (under target 3.3, 'leave no one behind'), but would also prove to be a cost-effective public health program both on a regional basis for currently affected countries and also on a wider, global scale.

Dengue viruses are four closely related but antigenically distinct serotypes: DENV-1, DENV-2, DENV-3 and DENV-4 (Leitmeyer *et al.*, 1999). They are all transmitted by mosquitoes within the Aedes genus (primarily *Aedes aegypti*),

which is most commonly found in Central and South America, Southeast Asia, the Caribbean and the Pacific Islands. After a person is bitten by an infected mosquito, the virus enters host cells by endocytosis and then replicates using the polymerase protein NS5, which acts as a capping enzyme for the viral RNA, thereby perpetuating the next stage of the virus life cycle when the replicated RNA leaves through the fusion pore where it will then utilise ribosomes to produce more viruses (Lim *et al.,* 2016). For the majority of cases, this will then result in dengue fever (DF) after a 4-10 day incubation period (Chan and Johannson, 2012) which is characterised by febrile symptoms, most commonly high temperatures, retro-orbital pain, nausea, polyarthralgia, myalgia and a macular or maculopapular rash. The critical phase then occurs after this 2-7 day febrile phase during which the majority of patients clinically improve. However, a smaller proportion of patients- around 96 million cases out of the estimated 390 million infections (Bhatt *et al.,* 2013)- with substantial plasma leakage may present a deterioration of symptoms.

This severe form of DF is classed as dengue hemorrhagic fever (DHF), manifesting itself through capillary leakage, which then leads to internal bleeding, fluid accumulation and respiratory distress. A small subset of DHF patients will then develop dengue shock syndrome (DSS), resulting in multiorgan failure such as myocardial failure, acute kidney failure, and more uncommonly neurological complications such as brachial neuritis (Verma *et al.,* 2011). DSS therefore results in mortality rates that can be as high as 26% (Suharti *et al*, 2009).

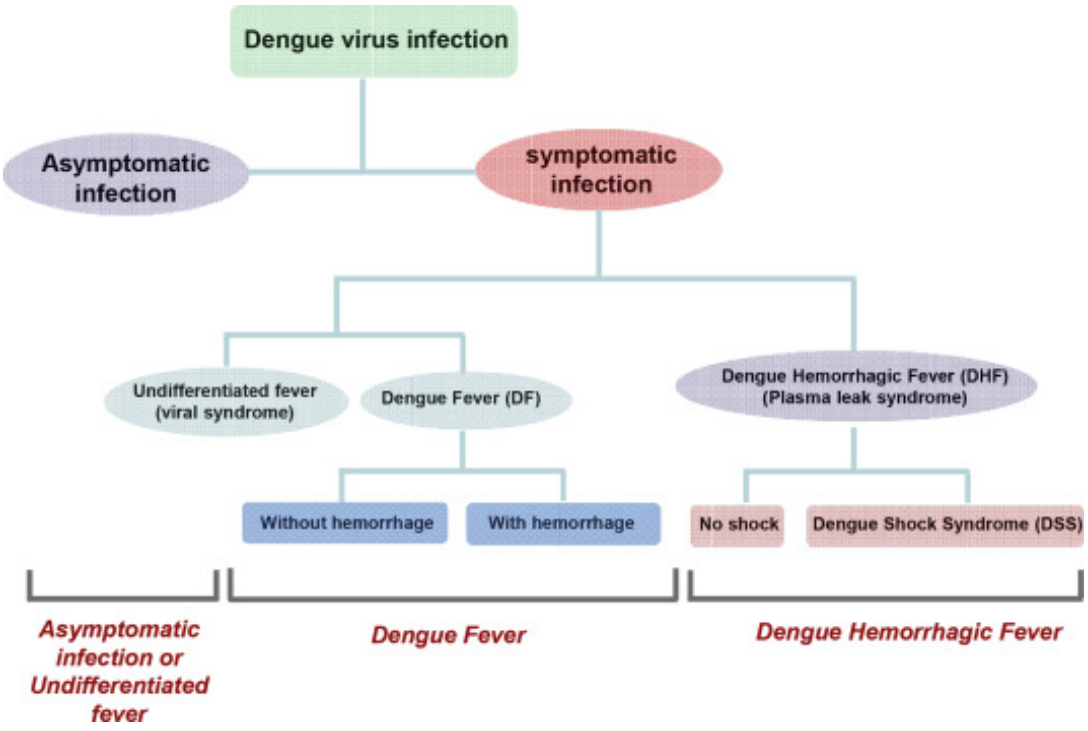


Figure 1. Classification of dengue infections (WHO, 1997)

Despite the potentially severe symptoms of DHF and DSS, current treatment in a clinical setting relies solely on supportive treatment, such as blood transfusions to combat thrombocytopenia, or administering intravenous fluids for rehydration (Rajapaske and Rodrigo and Rajapaske, 2012). The only recommended drug to relieve the symptoms of DF is paracetamol- even though the mortality rate for DHF can reach an annual 40 000 deaths (Xeng *et al.*, 2017). This absence of specific, curative treatment despite the clear consequences highlights the indispensable requirement for an antiviral to treat dengue.

One of the main risk factors for developing DHF is a previous infection of a distinct dengue serotype (Guzman and Alvarez and Halstead, 2013). This

would result in a higher viral load through extrinsic and intrinsic antibody dependent enhancement (ADE). The antibodies generated from the immune response to the different dengue serotype recognise and so bind to the subsequent dengue serotype, but instead of neutralising the virus, the heterotypic antibodies enhance the ability of the virus to enter host cells through the interaction of the virus-antibody complex with Fcγ or complement receptors on host cells. The internalised virus-antibody complex then heightens virus production by the inhibition of type 1 interferon and then the activation of interleukin-10 biosynthesis (Narayan and Tripathi, 2020). The two pathways can therefore act in combination to increase the viral load and so the severity of the disease. Consequently, the effects of ADE should not be overlooked in the production of a drug to combat dengue- as was demonstrated by the CYD-TDV vaccine in 2016 (commercially Dengvaxia). In November of 2017, nearly two years after the mass immunisation of 800 000 children in the Philippines with this vaccine, Sanofi then declared that Dengvaxia could actually result in a 'more severe disease' (Sanofi, 2017) in those children who had not previously been infected- and subsequently the vaccine programme was temporarily suspended.

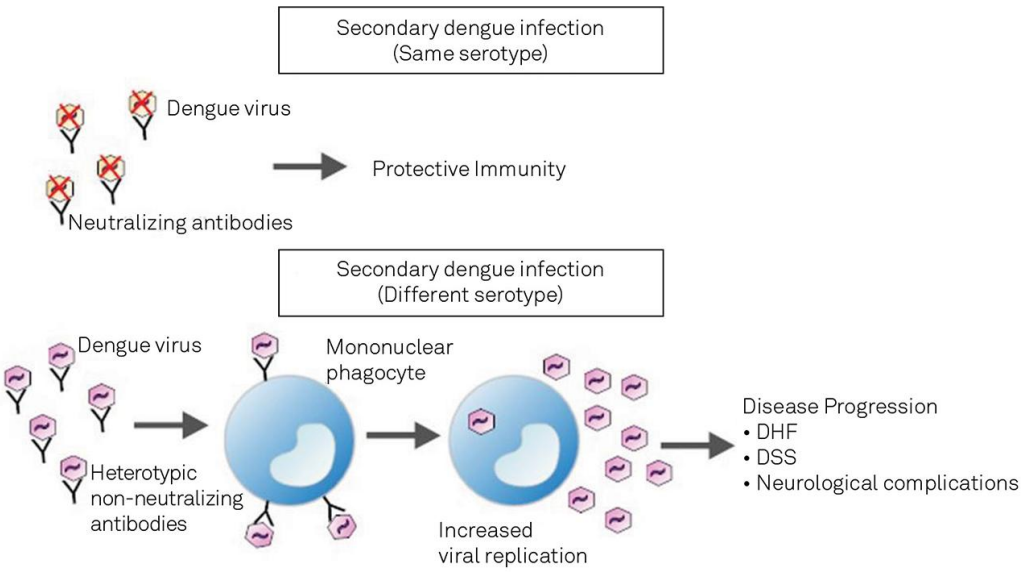


Figure 2. ADE in a dengue virus infection (Puccioni-Sohler and Rosadas, 2015).

The combined knowledge of the current treatments, the aetiology and the epidemiology of DF, DHF and DSS all act as indications of what an antiviral for dengue should be. The absence of a specific curative treatment and the risk posed by the current vaccine counters a symptomatic or prophylactic approach, as this either does not solve the underlying cause or leads to ADE. Therefore, a curative antiviral (that ideally responds to all four serotypes) would be a more effective drug as it avoids both of these issues. The aetiology then indicates how this antiviral could be developed: through modifications of existing antivirals, such as Sofosbuvir. Sofosbuvir is an antiviral used to treat hepatitis C, another flavivirus, by inhibiting the NS5 polymerase enzyme in order to prevent viral replication, subsequently disrupting the virus life cycle. A similar NS5 enzyme is also a fundamental part of the dengue virus life cycle (Potisopon *et al.*, 2014), and so modifications to this antiviral could produce a polymerase inhibitor effective against dengue virus. Finally, epidemiology foregrounds the importance of an economically viable drug. A mass immunisation programme for the 3.9 billion at risk (Brady *et al.,* 2012) would

be financially unsustainable- especially as Dengvaxia costs US$78 per individual (Pearson *et al*, 2019). In comparison, responding to 96 million individuals who annually develop DHF (Bhatt *et al.,* 2013) would be significantly more sustainable.

The consideration of the financial cost of a drug is also fundamental given the economic burden that is already present, not only as the estimated global cost of dengue illness in 2013 was US$8.9 billion (Shepard *et al*., 2016), but this is concentrated in low and middle income countries. While a large amount of this relates to the prevention costs, 40% of the estimated cost was attributed to lost productivity costs, which would serve to worsen the economic state of the affected countries, further perpetuating socioeconomic inequality by limiting economic growth. The socioeconomic effects are a clear indicator of the imperative need for an antiviral for dengue for countries currently facing an endemic, and future projections only serve to further stress the significance of a drug for dengue.

This is because although dengue is currently only a major threat to tropical and subtropical countries, the increasing global temperature and shifting rainfall patterns could expand the habitat of the Aedes mosquito to areas that are currently low-risk, such as Europe, North America, North Asia and Australia, thereby enabling transmission of dengue to a greater number of countries. In fact, this expansion has already been recorded in 2012 when the Portuguese island of Madeira faced 1080 autochthonous confirmed cases during their first-ever recorded dengue outbreak (Auerswald *et al*., 2012). Even despite emissions control, modelling suggests that the world would

become 3.2% 'more suitable' for *Aedes aegypti* each decade until 2050 (Iwamura and Guzman-Holst and Murray, 2020). This will then result in the dengue virus expanding to place 60% of the global population at risk of infection by 2050- and so the global risk of suffering from DF, DHF and DSS will only increase.

In light of the burden that dengue virus currently places on neglected developing countries and the future burden that will affect even more people, if I could invent a new drug it would be a curative antiviral for dengue (such as a polymerase inhibitor). By doing this I would not only combat the overlooked 40 000 annual deaths and the current US$8.9 billion economic cost, but also prevent any rise in these figures as the virus inevitably expands across the world.

## Reference List

Auerswald, H., *et al.* (2019) First dengue virus seroprevalence study on Madeira Island after the 2012 outbreak indicates unreported dengue circulation, *Parasites & vectors*, vol.12, no.1, pp.103. Available from: https://doi.org/10.1186/s13071-019-3357-3

Bhatt, S., *et al.* (2013) The global distribution and burden of dengue, *Nature*, vol.469, no7446, pp.504-507. Available from: https://rdcu.be/cKe8B

Chan, M., Johanasson, M. (2012) The incubation periods of Dengue viruses, *PLoS One*, vol.7, no.11, e50972, available from: https://doi.org/10.1371/journal.pone.0050972

Gubler, D. (2002) Epidemic dengue/dengue hemorrhagic fever as a public health, social and economic problem in the 21st century, *Trends in microbiology*, vol.10, no.2, pp.100-103. Available from: https://doi.org/10.1016/s0966-842x(01)02288-0

Guzman, M., Alvares, M., Halstead, S. (2013) Secondary infection as a risk factor for dengue hemorrhagic fever/dengue shock syndrome: an historical perspective and role of antibody-dependent enhancement of infection, *Archives of virology*, vol.158, no.7, pp.1445-1459. Available from: https://doi.org/10.1007/s00705-013-1645-3

Iwamura, T., Guzman-Holstm A., Murray, K. (2020) Accelerating invasion potential of disease vector *Aedes aegypti* under climate change, *Nature communications*, vol.11, no.1, 2130. Available from: https://doi.org/10.1038/s41467-020-16010-4

Leitmeyer, K. C., *et al.* (1999) Dengue virus structural differences that correlate with pathogenesis, *Journal of virology*, vol.73, no.6, pp.4738-4747. Available from: https://doi.org/10.1128/JVI.73.6.4738-4747.1999

Lim, S., *et al.* (2016) Potent Allosteric Dengue Virus NS5 Polymerase Inhibitors: Mechanism of Action and Resistance Profiling, *PLoS Pathog*, vol.12, no.8, e1005737. Available from: https://doi.org/10.1371/journal.ppat.1005737

Lo, C. (2019) The dengue vaccine dilemma, *Pharmaceutical technology*. Available from: https://www.pharmaceutical-technology.com/features/dangvaxia-philippines/

Madewell, Z. (2020) Arboviruses and their vectors, *Southern medical journal*, vol. 113, no.10, pp.520-523. Available from: https://doi.org/10.14423/SMJ.0000000000001152

Narayan, R., Tripathi, S. (2020) Intrinsic ADE: The Dark Side of Antibody Dependent Enhancement During Dengue Infection, *Frontiers in cellular and infection microbiology,* vol 10, 580096. Available from: https://doi.org/10.3389/fcimb.2020.580096

Pearson, C., *et al.* (2019) Serostatus testing and dengue vaccine cost–benefit thresholds, *Journal of the Royal Society*, Interface, vol.16, no.157, 20190234. Available from: https://doi.org/10.1098/rsif.2019.0234

Potisopon, S., *et al.* (2014) Comparison of dengue virus and HCV: from impact on global health to their RNA-dependent RNA polymerases, *Future virology*, vol.9, no.1, pp.53-67. Available from: https://doi.org/10.2217/fvl.13.121

Puccioni-Sohler, M., Rosadas, C. (2015), Advances and new insights in the neuropathogenesis of dengue infection. *Arquivos de neuro-psiquiatria*, vol.*73, no.*8, pp.698–703. Available from: https://doi.org/10.1590/0004-282X20150074

Rajapakse, S., Rodrigo, C., Rajapakse, A. (2012), Treatment of dengue fever, *Infection and drug resistance*, vol.5, pp.103-112, available from: https://doi.org/10.2147/IDR.S22613

Sanofi. (2017) Sanofi updates information on dengue vaccine press release. Available from: https://www.sanofi.com/-/media/Project/One-Sanofi-Web/Websites/Global/Sanofi-COM/Home/media-room/press-releases/2017/2017-11-29-17-36-30-1210526-en.pdf

Suharti, C., *et al.* (2009) Risk factors for mortality in dengue shock syndrome (DSS), *Media Medika Indonesiana*, vol. 43, no.5 , pp. 213-219.

Verma, R., *et al.* (2011) Neurological complications of dengue fever: Experience from a tertiary centre of north India, *Annals of Indian Academy of Neurology*, vol.14, no.4, pp.272–278. Available from: https://doi.org/10.4103/0972-2327.91946

WHO. (1997) Dengue hemorrhagic fever: Diagnosis, Treatment, Prevention and Control, 2nd edition, *World Health Organisation,* Geneva.

Zeng, Z., *et al.* (2021), Global, regional, and national dengue burden from 1990 to 2017: A systematic analysis based on the global burden of disease study 2017, *EClinicalMedicine*, vol.32, no.100712. Available from: https://doi.org/10.1016/j.eclinm.2020.100712