should be put in place. Distribution of dengue detection kits to health centres and training of health facilitators would be beneficial in rural areas. Since personal clothing acts as a preventive measure, a special focus should be given to school children through the improvement of school uniform. Mass media could act by disseminating information about dengue phases, use of bednets and mosquito repellents, and wearing of clothing that light coloured, loose fitting, long sleeved, and breathable.

Long-term sustainable control of dengue virus is essential to manage future outbreaks. Actions that could be taken include nationwide event-based dengue surveillance with environmental management; research on ecological, environmental, and entomological indicators of infection; development of geospatial and risk mapping for scoping vulnerable zones;[1] involvement of researchers to capture data on the trend and virus evolution over the geographical time period, considering seasonal influences and the impact of climate change;[1] and the implementation of inexpensive and accessible bioassay systems for early detection of dengue, especially in rural areas. In addition, a dengue virus vaccine could be launched in the country as it has been shown to reduce severity and hospital admissions by 80–90% among children in Asia.[5]

In addition to existing national guidelines from the Directorate General of Health Services in Bangladesh, we suggest the development of a national dengue control programme for clinical management of the infection, alongside a widespread community awareness campaign for greater responses. Although the government of Bangladesh has initiated some short-term measures, mainly in Dhaka, countrywide comprehensive action measures have been inadequate. The government and relevant stakeholders should prioritise this dengue outbreak and adopt a holistic dengue control programme to prevent premature deaths and reduce the disease burden of this epidemic.

We declare no competing interests.

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Suboptimal dosing triggers artemisinin partner drug resistance

3-day artemisinin-based combination therapy regimens are the treatment of choice for most cases of uncomplicated malaria. Their efficacy relies on artemisinin to clear most of the parasite load. The mechanism of action of artemisinin requires activation by haem, resulting in promiscuous targeting of parasite proteins, ensuring both specificity and potency to deliver unrivalled antiparasitic activity.[1]

Artemisinins are cleared relatively rapidly from circulation (usually in a few hours, depending on the derivative and formulation), a property that presents a weakness to parasites. This relatively short-term exposure to the drug has resulted in a selection of parasites carrying mutations in the propeller domain of the *kelch13* genes that are associated with extended ring stages of development.[2] This global developmental adjustment in lifecycle allows parasites to outlast the short-lived artemisinin component of artemisinin-based combination therapies, rather than causing treatment failures because of selection for conventional resistance.

Because 3-day courses of artemisinin do not cure infections, even those with so-called artemisinin-sensitive parasites, 3-day artemisinin-based combination regimens depend on a partner drug to achieve a complete cure. When faced with parasites with altered lifecycles, partner drug-resistance associated with treatment failures is then attributed to so-called artemisinin resistance, as reported by Rob van der Pluijm and colleagues[3] in the Greater Mekong subregion. When dihydroartemisinin–piperaquine treatment did not cure infections, van der Pluijm and colleagues found that a new combination of dihydroartemisinin–piperaquine–mefloquine increased efficacy.[3] However, dihydroartemisinin might be relatively less stable than artesunate in drug formulations,[4] and adding a third partner drug that is itself selecting for resistance might not provide a sustained advantage if the artemisinin component is not dosed optimally.

More effective measures must be taken immediately. In the short term, several artemisinin-based combination therapies (eg, artesunate plus pyronaridine and artesunate plus mefloquine) that are effective in geographical areas with parasites that

For the **guidelines from the Directorate General of Health Services** see http://www.dghs.gov.bd/images/docs/Guideline/NationalGuidelinefor Dengue2018.pdf

do not fully respond to treatments with dihydroartemisinin–piperaquine should be recommended. In the long term, we must optimise current artemisinin-based combination therapies and investigate potentially increasing the duration of artemisinin administration. Focusing on triple combination therapies could become a distraction and miss a crucial opportunity to achieve urgent elimination of malaria parasites before new complications arise.

SK is a member of the WHO Malaria Treatment Guidelines Group. This group produces global guidance on the treatment of malaria and this includes decisions on artemisinin combination therapies. The views expressed here are personal opinions and do not represent the recommendations of WHO. All other authors declare no competing interests.

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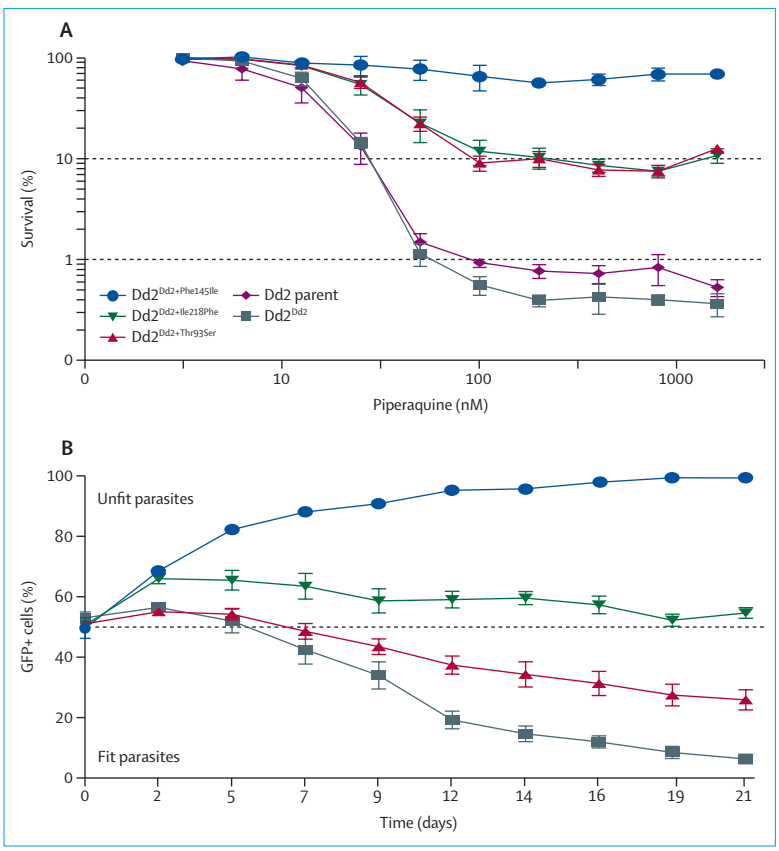

Figure: **Piperaquine survival and fitness of *pfcrt*-edited lines**
(A) Survival of *pfcrt*-modified parasite lines cultured with various concentrations of piperaquine (0–6 h rings, treated for 48 h). The 10% cutoff represents a standard working threshold for piperaquine resistance at 200 nM piperaquine. Data are mean with SEM for three to four independent assays done in duplicate. (B) In-vitro growth of the indicated parasite lines in competition with a GFP-positive reporter line. Data are mean with SEM for two independent experiments done in triplicate. Methods are provided in the appendix. GFP=green fluorescent protein.

See Online for appendix

Plasmodium falciparum resistance to piperaquine driven by PfCRT

The Articles by William Hamilton and colleagues[1] and Rob van der Pluijm and colleagues[2] illustrate the plummeting clinical efficacy of dihydroartemisinin–piperaquine as a first-line treatment for *Plasmodium falciparum* malaria in southeast Asia. These authors also report a rapid regional spread of clonal parasite lineages harbouring novel variants of the *P falciparum* chloroquine resistance transporter PfCRT (emerging on the chloroquine-resistant Dd2 isoform). These lineages exclusively harboured the Cys580Tyr mutation in the *K13* gene that is associated with decreased artemisinin efficacy. These studies raise important questions about whether these novel PfCRT variants cause piperaquine resistance, how they effect other antimalarials, and whether changes in prevalence over time reflect differences in parasite fitness.

Here, we show that the now predominant PfCRT Thr93Ser and Ile218Phe mutations, which of all mutations have expanded the most rapidly in the past 5 years,[1,2] confer piperaquine resistance when individually edited into the *pfcrt* locus of Dd2 parasites. Assays with cultured intra-erythrocytic parasites show 8–13% survival at piperaquine concentrations ranging from 200 nM to 1600 nM (figure; appendix p 5). The Phe145Ile mutation was highly piperaquine-resistant, with 57–69% survival at these elevated concentrations, consistent with previous findings.[3] Parental or control Dd2 parasites with an edited *pfcrt* showed less than 1% survival, reflecting background