Reply to Padhi et al

To the Editor—Coronavirus disease 2019 is characterized by endotheliitis and vasculitis [1, 2], which has been repeatedly reported to be associated with the intercellular adhesion molecule 1 (ICAM-1) K469E polymorphism, as in coronary artery disease [3], type 1 diabetes [4], and inflammatory bowel disease [5]. In their letter [6], Padhi et al report that ICAM-1 K469E polymorphism was positively correlated with a higher possibility of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and related mortality rate, thus concluding that ICAM-1 variants may play a role in susceptibility to SARS-CoV-2 infections and increased chances of death.

However, it is necessary to interpret this conclusion prudently. Aside from the genetic polymorphism, the uneven infection rate could be influenced by imbalances in the government management ability to deal with public health emergencies (emergency response ability of primary health institutions, information level, international cooperation, implementation of effective isolation measures) [7], the supply of SARS-CoV-2 testing reagents, the willingness of the public for screening, and the scope of vaccination. Similarly, in addition to genetic factors, the diverse mortality rates may be affected by many factors, such as unequal healthcare systems [8], different methods of calculating mortality rates (deaths directly or indirectly related to SARS-CoV-2 infection), preexisting diseases [9], virus variants, and demographic characteristics (male sex and older age are associated with higher mortality rates) [10].

Therefore, based on the considerations above, the study by Padhi et al provides only preliminary assumptions regarding the correlation among ICAM-1 K469E polymorphism, susceptibility to SARS-CoV-2 infection, and related mortality rates. Thus, as the authors noted, a successful case-control study is necessary to explore the associations.

Notes

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Regarding "The Clinical and Economic Burden of Norovirus Gastroenteritis in the United States"

To the Editor—In their recent article, Bartsch et al report the calculated economic costs of rotavirus infection in the United States using a Monte Carlo simulation model [1]. This study importantly

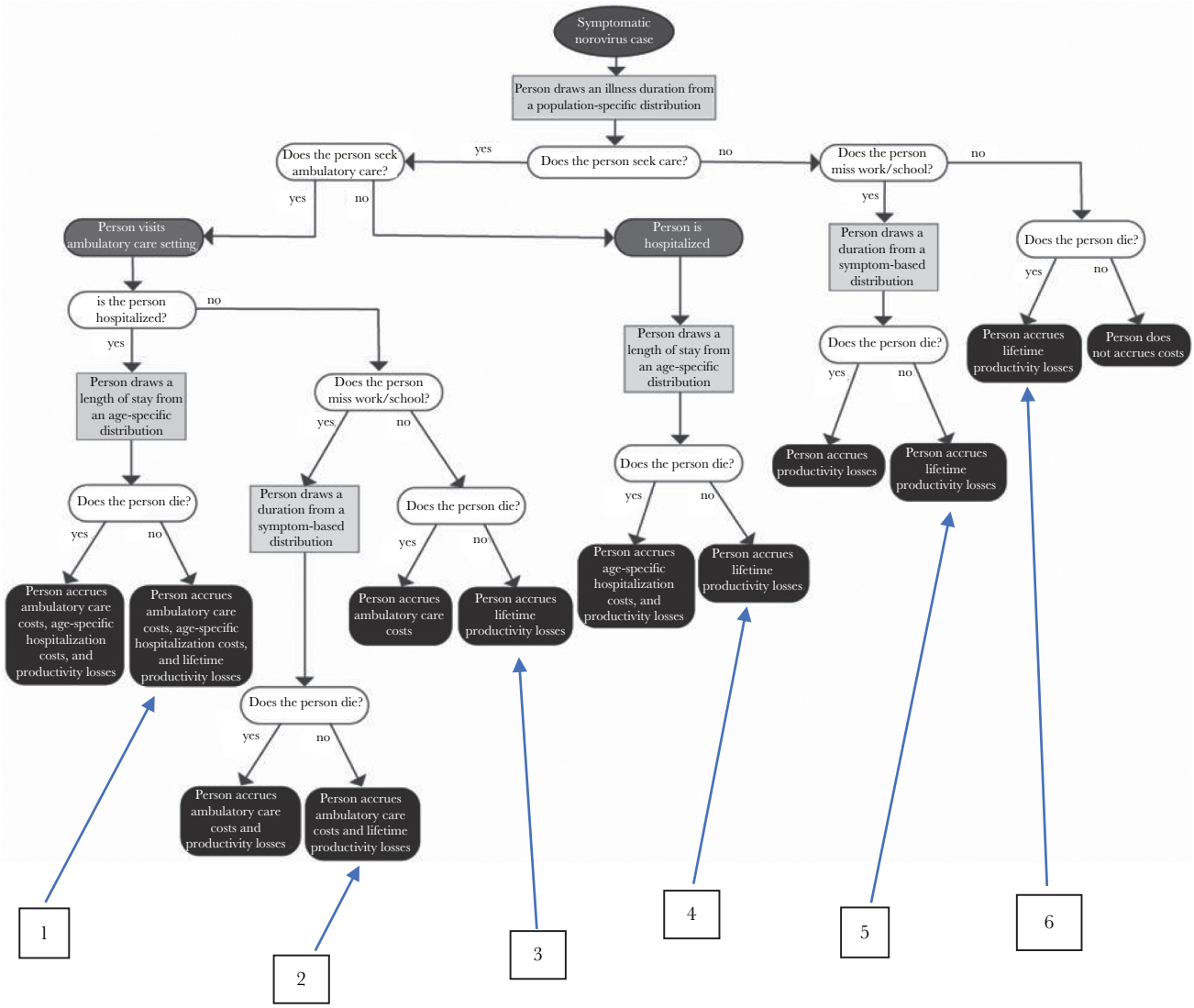

Figure 1.

concludes that rotavirus infection produces a heavy economic burden on the healthcare system in the United States. The authors' Monte Carlo simulation decision tree (Figure 1) evaluates several parameters from established data sources and estimates the cost of norovirus illness through the model. Included in their analysis is productivity loss for both time of illness and if death occurs.

After reviewing the decision tree, we are concerned that an error occurred in either the decision tree figure, the Monte Carlo simulation calculations, or possibly both. Our specific point of concern involves the branch point where a patient lives in the algorithm. In 5 of the 6 times where this branchpoint occurs, the figure indicates that survival is associated with lifetime productivity losses for the patient (labeled 1–5). We believe that death would be associated with lifetime productivity losses and that the figure is incorrect. However, in 1 of the 6 times where this branchpoint occurred, it is death that is associated with lifetime productivity losses (labeled 6). These discrepancies lead us to be concerned that 1 or more of the Monte Carlo simulation calculations could have been run in error.

We think it would be prudent for the authors to reevaluate the decision tree figure and recheck the underlying equations used for their Monte Carlo simulation to clarify if any errors occurred.

Notes

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Questioning the Claimed Superiority of Malaria Parasite Ex Vivo Viability Reduction Over Observed Parasite Clearance Rate?

To the Editor—In a study of 10 *Plasmodium falciparum*–infected volunteers with submicroscopic parasitemias given a single 200-mg dose of artesunate, Rebelo et al [1] reported a substantial difference in the ex vivo growth of sequentially sampled circulating ring-stage [2] parasites comparing infections with artemisinin-sensitive (Pfkelch wild-type) and artemisinin-resistant (Pfkelch R539T) parasites. In the 5 artemisinin-sensitive infections, they derived an estimated ex vivo mean parasite "viability" reduction half-life of 0.75 hour, considerably shorter than the corresponding 3.2-hour in vivo mean parasite clearance half-life estimate. In contrast, in the 5 artemisinin-resistant infections, the mean estimated viability reduction half-life was 8.7 hours, compared with 6.5 hours for the in vivo parasite clearance half-life.

This observation is consistent with numerous laboratory studies showing that artemisinin resistance in *P. falciparum* is associated with loss of ring-stage susceptibility [3–6]. Indeed, this clinical study can be considered as a rather laborious in vivo ring-stage survival assay [4]. The "viability" effect measure is derived from the subsequent ex vivo growth of malaria parasites following different drug exposures. The reduction in viability reflects the damage done by the drug exposure in vivo, and any parasite sequestered antimalarial drug in the ex vivo culture, and the continued effects of that damage. This was compared with the serial parasite densities at the time of blood sampling, which are used to provide a parasite clearance rate [7].

The serial quantitative polymerase chain reaction derived parasitemia profiles shown by Rebelo et al [1], fig 3 strongly suggest continued input into the circulation from ongoing schizogony [2, 8]. This explains why parasite densities in blood do not fall for approximately 8 hours. The most commonly used parasite clearance rate estimator explicitly accounts for this lag-phase [7]. In contrast, the viability estimates use blood samples containing circulating parasites and high artesunate concentrations, and much of the effect is observed by the first sampling time point (2 hours). Taking a blood sample and diluting out the antimalarial drug does not instantly stop it working. Parasites take time to die, so it is not surprising that the ex vivo assessment over days suggests greater "killing" than the densities of parasites in the blood at the time of sampling would suggest, but to conclude that "parasite resistance to artemisinins may have a more profound effect on in vivo drug efficacy than previously appreciated" is not warranted. If this means that parasite killing by artemisinins has been underestimated, then it is not compatible with clinical trial observations of the relationship between dosing, duration of treatment, and outcome [9].

The title of the article, "Parasite viability as a superior measure of antimalarial drug activity in humans" [1], suggests a significant advance, but it is not clear why or how it would be used to assess antimalarial drugs. It is stated that "the use of parasite clearance to measure drug activity and to inform decisions about drug development should be reconsidered in view of these new insights." It is unclear what these insights are and whether these difficult and laborious serial in vivo studies would offer any advantage over the currently used, simple ring-stage in vitro tests [4, 6], which identify the loss of ring-stage activity in artemisinin-resistant parasites very well.

The meaning and predictive value of the estimated half-life from the viability studies are also unclear. The observed log-linear decline in parasite densities in blood after artemisinin treatment provides a clearance half-life of about 3.5 hours, which, if continued, would result in an approximately 16 000-fold decrease per life-cycle. This predicts that ≥5 days of artemisinin monotherapy (regardless of dosing frequency) are needed to clear an infection with a biomass of 10^{12} parasites. This matches clinical observations [9]. But what is the meaning or utility of the half-life estimated from the viability study? Interpreted literally, a continued half-life of 0.75 hours would kill all the infecting malaria parasites within a day, which clearly does not match clinical observations.

As for dose finding, the results presented in [1] fig 3 suggest that the fits to the serial viability log-linear declines are poor and, thus, the derived viability half-lives are imprecise in comparison with the parasite clearance profiles. Indeed, it is unclear whether declines are exponential and, therefore, whether the model is appropriate. This does not give confidence that a concentration-effect (dose-response) estimate derived from these