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Our Policy Forum is not a risk-benefit analysis; it does not, as Streicker *et al.* assert, caution that the risks of self-spreading vaccines outweigh the benefits, and we do not call for "tighter regulation." We are calling for engagement and evidence-based debate in appropriate technical and political forums.

Although we agree with Streicker *et al.* that vaccine hesitancy is an important concern in the current pandemic, we disagree that the timing of our call for discussion is problematic. Rather, it is the lack of ethical discussion and public engagement on the far-reaching implications of self-spreading vaccines that is likely to reduce public trust. This is particularly pressing due to ongoing development in the absence of debate.

Streicker *et al.* argue that preventing zoonotic spillover "is an unlikely first step" for self-spreading vaccines. Yet it is clearly a goal. For example, the ongoing PREEMPT program, funded by the US Defense Advanced Research Projects Agency (DARPA), aims to target animal pathogens before they are "adapted to become capable of infecting humans" (1). Our view is that all proposed applications should be part of the debate.

Streicker *et al.* present reduced cost as a benefit of self-spreading vaccines. However, all human and veterinary vaccines must complete rigorous licensing processes, which represent a substantial proportion of the cost of vaccine development. Self-spreading vaccines would be subject to these standards, and therefore costs, as well. Despite ongoing development, as we explain in our Policy Forum, there are no articulated proposals for regulatory pathways to establish self-spreading vaccines as safe, effective, useful, and publicly trusted.

According to Streicker *et al.*, more investment should be directed to the development of self-spreading vaccines. If this is to be the case, we urge funders and developers who choose to work on self-spreading vaccines to publicly commit to use them to address needs within their own borders. Currently, applications in other nations are used to motivate development activities, and field trials are being proposed in overseas countries. Keeping applications and initial field trials within the borders of where the research originates will maximize the chances of sufficiently robust debate among fellow citizens and nations about the wisdom of self-spreading viral approaches in the

1. DARPABiologicalTechnologiesOffice, "BroadAgency Announcement PREventing EMerging Pathogenic Threats (PREEMPT), HR001118S0017" (2018), pp. 4–5; https://assets.ctfassets.net/syq3snmxclc9/6K3RxB1D Vf6ZhVxQLSJzxl/6be5c276bc8af7921ce6b23f0975a6 c3/A_prempt-background-hr001118s0017.pdf.