We welcome the letter by Streicker *et al.* (1) and the opportunity it affords to engage.

While vaccine-hesitancy is a significant concern in the current pandemic, and one we take very seriously, we find its linkage with self-spreading vaccines has little merit. It is not the timing of our call for discussion that is problematic; it is self-spreading vaccines themselves (11), and the lack of ethical discussion and public engagement on their far-reaching implications, that is likely to reduce public trust in vaccines. Dialogue is a vital ingredient in building and sustaining trust, which can take years to build and a moment to break.

Indeed, we find it illuminating that a letter (1) by three prominent advocates for self-spreading vaccines not only strikingly omits their previously persistent claim that viral evolution can now be fine-tuned or even suspended (3-6), but that they present cost as the primary value of self-spreading vaccines. A cost-based argument can only be made in relation to vaccines with conventional deployment strategies (e.g. yellow fever) or oral-bait vaccines (e.g. rabies). In the modern era, all human and veterinary vaccines must successfully complete rigorous national and often supra-national licensing processes, and these represent a substantial proportion of the cost of vaccine development. It is inconceivable that self-spreading vaccines would be subject to lower safety and efficacy standards—and licensing costs—than conventional vaccines.

We also fail to see how the subjective question of whether a self-spreading vaccine developed "using a benign, naturally occurring viral vector" (1) is substantively different from the rabbit vaccine developed and field-tested more than 22 years ago (7,8), which also utilizes a viral vector (a weakly pathogenic isolate that was circulating in the area of its proposed use) (3). The relevance of this first self-spreading vaccine to what is currently being proposed is underscored by the fact that Streicker *et al.* have cited at least one of three papers describing the Spanish vaccine (7-9) no less than 19 times in their own publications. This includes citing two of the three (7,8) as establishing the "efficacy and safety" of self-spreading vaccine technologies (10).

Unlike Streicker *et al.*, we believe there are multiple important connections between self-spreading vaccines and a range of proposals for other viral technologies that are intended to be self-spreading in the environment. These include ones to protect, sterilize or kill vertebrate wildlife populations. Furthermore, evidence from both unintended viral releases and natural epidemics will be critical to factor into efficacy and safety evaluations, as recognised by CBD experts in 2007 (2).

Finally, we note with some disappointment that the letter contained no reference to initiatives by Streicker *et al.* to initiate discussions to resolve outstanding questions about: the lack of evidence for suppressed viral evolution and predetermined lifetimes in self-spreading vaccines; anticipated benefits, possible harms and risks, and appropriate precautionary measures; and credible pathways that could establish self-spreading vaccines as safe, effective and publicly trusted (12,13). In this light, we make the following three proposals:

1. Funders and developers of self-spreading vaccine research should host debates on self-spreading vaccines, encouraging participation by peers, policymakers and the wider public—without suggestions of insufficient expertise to participate.
2. Speculations should be minimized on both on the outward value of self-spreading vaccines in humans (3,4,14) and whether any currently licensed human vaccines can meaningfully be described as self-spreading (3,6) as we define them (15).
3. Funders and developers that choose to work on self-spreading vaccines should 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 chances of sufficiently robust debate among fellow citizens and nations about the wisdom of self-spreading viral approaches in the environment.

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