Title: Developing transmissible vaccines for animal infectious diseases

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Main text:

Many emerging and re-emerging pathogens originate from wildlife, but nearly all wild species are unreachable using conventional vaccination, which requires capture of and vaccine administration to individual animals. By enabling immunization at scales sufficient to interrupt pathogen transmission, transmissible vaccines (TVs) that spread themselves through wildlife populations by infectious processes could potentially transform management of otherwise intractable challenges to public health, wildlife conservation, and animal welfare. However, generating TVs likely requires modifying viruses that would be intended to spread in nature, raising concerns ranging from technical feasibility, to safety and security risks, to regulatory uncertainties (*1*, *2*). We propose a series of commitments and strategies for vaccine development, beginning with *a priori* decisions on vaccine design and continuing through to stakeholder co-development (see the box), that we believe increase the likelihood that the potential risks of vaccine transmission are outweighed by benefits to conservation, animal welfare, and zoonosis prevention.

The inability to control emerging pathogens at their source translates into mitigation strategies focused on direct protection of humans or domestic animals, an approach that fails to curb the risks and costs of recurring transmission between species (hereafter, spillover). Diseases threatening wildlife health, either through recurrent spillover (e.g., Ebola in great apes) or following host shifts and/or pathogen translocations (e.g., white nose syndrome [WNS] in bats), remain similarly uncontrollable by conventional approaches. Mass distribution of oral vaccines via baits has shown that scalable vaccination of wildlife can protect human health and animal welfare; however, bait delivery systems are incompatible with many wild species (*3*).

TVs have been proposed as a scalable, low-cost option to interrupt transmission within and to otherwise unreachable wildlife *(4)*. However, risks of vaccine transmission are well recognized from theory and have been substantiated in conventional vaccines that transmit inadvertently (Figure 1). Most notoriously, sustained transmission of the live attenuated oral polio vaccine enabled reversion to its ancestral polio-causing phenotype. Although deliberate vaccine transmission has only rarely been tested, a vaccine against rabbit hemorrhagic disease (RHD) did explore the possibility using an attenuated myxomavirus-based vaccine (*5*). Although no ill effects were reported prior to natural vaccine extinction, the myxomavirus used was not host specific and had only a brief co-evolutionary history with the target rabbit species, making its long-term evolutionary trajectory uncertain. Recent interest in TVs has been revitalized by accumulating evidence that it may be possible to design vaccines that mitigate foreseeable risks while preserving efficacy. Such TVs are currently being advanced in laboratories, but to our knowledge, none have been released in any natural population.

The relative lack of substantive public discourse involving both proponents and critics of TVs has created a scientific landscape with conflicting definitions and immaterial evidence that is unhelpful for policymakers, funders, and the organizations charged with oversight of the research and development process. As a group of bioethicists, disease ecologists, evolutionary biologists, immunologists, sociologists, and virologists, including both proponents and critics of TVs, we appraised the potential ecological and societal risks arising from transmission of an engineered viral vaccine (see supplementary materials). The commitments that arose are not intended to establish dogma or legitimize the use of TVs but rather to serve as a conservative starting point which we expect will evolve with societal attitudes, scientific evidence, and technology.

INTRINSICALLY SAFE, BIOLOGICALLY COMPELLING VACCINE DESIGNS

Flexible vaccine designs are most easily accommodated using recombinant vaccines that consist of two parts engineered into one genome: a relatively benign animal virus (the vector) and a short genetic segment from the pathogen (the antigenic insert or transgene), which induces an immune response. The goal is to preserve the capacity for transmission between individuals, while adding the ability to immunize, thereby magnifying the vaccination coverage derived from each directly vaccinated individual.

As vaccine safety hinges predominately on the properties of the vector, we propose eligibility criteria. First, vaccines derived from cross-species transfer (e.g., myxomavirus-based RHD vaccine) may spread unpredictably causing ecological disruption. New selective environments, including the possibility of novel co-infections with recombination-compatible viruses, might also promote evolution towards previously unobserved, harmful phenotypes (*5*). Vectors would therefore need to be both isolated from and returned to their natural host species. Because competition between TVs and their ancestral (wildtype) or descendant (reversion to non-vaccine strain) viruses may inhibit vaccine spread, vectors that can infect hosts with prior or concurrent wildtype infections are desirable. Alternatively, competition with the wildtype may be overcome by repeatedly introducing the vaccine or constructing it using locally rare or absent strains (*6*, *7*).

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Second, vaccines that cross species boundaries during transmission in nature present similar risks to deliberate cross-species transfer. Vectors would therefore need to be host specific, as demonstrated by representative surveys for cross-species infections in nature, co-evolutionary analyses supporting host-virus co-speciation over host switching, laboratory studies of cellular tropism, and animal inoculation studies. Ecologically plausible exposures in sympatric, non-target species (i.e., those that are not part of the planned vaccination campaign) would need to lead to insufficient replication to cause clinical disease or vaccine transmission. Ecological plausibility might be derived from local knowledge, expert opinion, and/or *in silico* predictions of susceptibility. In cases where multiple host species independently maintain the pathogen and a single viral vector infects these species, safety and efficacy studies should include all relevant hosts.

Third, viruses that would require attenuation (reducing virulence) to align with management goals and stakeholder desires are excluded since perturbing the co-evolved virus-host equilibrium might select for a return to the undesirable ancestral state (fig. S1). Unlike reversion of attenuated vaccines, reversion of TVs to their ancestral phenotype creates no novel health or environmental risks because the ancestral virus naturally circulates in the same host species. This strategy also alleviates the potential concern that TVs could gain pathogenicity by recombining with wildtype strains (*8*).

Misuse of the knowledge acquired during the development of new technology is always a concern. Consistent with the core ideology of exploiting natural traits of viruses as built-in safety features, engineering of viral vectors would avoid modifications that increase host range, pathogenicity, or transmissibility. More generally, any technology that could plausibly be harmful if applied to a human-infecting virus should be avoided in TVs designed for animals. For instance, discovering novel molecular mechanisms that augment spread or enhance evolutionary stability might benefit vaccine coverage but could have malicious applications elsewhere. If increased stability is required to reach management objectives, methods could be limited to transgene identity, size, copy number, and placement (*9*). Alternatively, more intensive or efficient deployment can increase coverage (*10*).

STAGED DEVELOPMENT WITH ESTABLISHED CHECKPOINTS

We believe the criteria described above maximize the safety of TVs without undermining their potential efficacy *(10,11)*. Nevertheless, unforeseeable issues may arise during the vaccine development process which may prompt suspension of a TV's development. A staged development process is needed for early identification and containment of emergent risks. Specifically, TV development would advance from *in vitro* studies in laboratories, to *in vivo* animal testing within appropriate biological containment, to limited trials in populations that are naturally (e.g., islands, mountains) or experimentally (e.g., enclosures, semi-field systems) isolated (Figure 1). Following an Open Science approach, quantitative benchmarks for safety and efficacy would be defined in advance and transparently shared as checkpoints to continue or not with a given vaccine candidate. Instability of recombinant TVs through silencing or purging of the transgene is expected and detrimental to efficacy but acts advantageously as a natural self-limiting mechanism against uncontrolled spread. When technically possible, vaccines themselves should be staged, with early experiments using vaccines expected to have a short evolutionary half-life, mitigating risks of prolonged circulation of an undesirable prototype in the event of laboratory escape.

Accountable systems to monitor vaccine release, evolution, and spread will be critical throughout the development process. These include re-sequencing of the vaccine to monitor evolutionary changes and periodic *in vitro* monitoring of growth rate or cellular tropism. Since vaccinated animals possess immunity only to pathogen proteins included within the antigenic insert, immunological monitoring could differentiate previously infected and vaccinated animals. The potential for vaccines to create secondary hazards, such as exposure to vehicles used in vaccine deployment (e.g., topical gels, baits, aerosols), also needs to be considered and monitored when appropriate. Researchers should establish contingency plans for foreseeable risks (noting that a contingency plan can include 'no action') and implement appropriate management systems for timely responses to unforeseen events.

EQUITABLE PARTNERSHIPS WITH INTERNATIONAL GOVERNANCE

While the impossibility of individual consent prohibits consideration of TVs for human use, complex ethical issues around consent also arise for TV use in animals. Concerns and requirements around technology development, staged delivery timelines, and identification of any ecological ramifications of reducing pathogen circulation would require reciprocal engagement with relevant stakeholders, including government agencies that regulate vaccine use in animals, wildlife population managers, public health officials, non-government agencies, and affected communities (‘co-development’). Initiating this process at project inception and certainly before engineering of vaccine prototypes benefits vaccine developers by identifying technical and community values-based constraints that would alter deployment or development targets (*12*). Communities affected by zoonotic spillover may desire rapid or geographically expanded TV deployment or, due to the novelty of TVs, may alternatively focus on potential risks while overlooking benefits. Scientists and communicators with expertise in managing expectations and identifying community champions will play a key role by ensuring that information about vaccine performance or safety is accurately portrayed, thus empowering communities to help make decisions with free, prior, and informed consent. Communication and engagement should also raise awareness of the potential for discussions of TVs to reduce acceptance of conventional vaccines, thereby inadvertently harming health.

As with any vaccine, TV development will be subject to existing local, national and international regulations for scientific research, production and testing, environmental impacts, and to funders’ discretion. One motivation for TVs is to reduce the disproportionate burden of pathogen spillover from wildlife in lower- and middle-income countries. It is therefore unavoidable that some developmental stages for some TVs (e.g., contained field trials) would be undertaken in these countries, while other stages (e.g., vaccine engineering and laboratory-contained animal trials) may be undertaken in countries with more funding and infrastructure. As regulatory requirements also vary across countries, stringent oversight as a shared, international responsibility underpins credibility, for example, requiring ethical and biosafety practices approaching the most conservative standard among partner nations involved. TVs developed to conserve wildlife may avoid the potential geographic mismatches between TV use and development. Greater investment in this area could provide valuable proof of concept for TVs targeting zoonotic spillover. Regardless of management targets, equitable collaborations, wherein risks taken and benefits gained are proportionate and undertaken by nationally diverse teams, are warranted across developmental stages.

TOWARDS DEPLOYMENT

In principle, TVs are suited to well-studied host-pathogen systems where spillover from established reservoir hosts is predictable, recurrent, and costly (e.g., rabies virus, Lassa fever virus, Nipah virus, Marburg virus) or where low-cost, scalable interventions could reduce pathogen threats to wildlife (e.g., WNS in bats, Ebola virus disease in non-human primates, retrovirus infection and Chlamydiosis in koalas). In practice, whether TVs are pursued over conventional alternatives should be evidence driven. For example, to evaluate whether host behavior or life history may constrain vaccine transmission to impractical levels, the maximum coverage that could be expected from a TV can be estimated from the proportion of individuals in target host populations that are naturally infected with the candidate viral vector. Similarly, the geographic extent of spread can be inferred from vector population genetics (*7*). Dynamic models derived from these data, and similar data describing the transmission dynamics of the target pathogen (including the potential roles of alternative host species in long-term maintenance), would be expected to support positive benefit-cost ratios of TVs over alternatives, whether through increased levels of vaccine coverage or improved immunological protection. When appropriate, models should consider sensitivity to vaccine reversion, reduced vaccine fitness from genetic manipulation, and competition with the wildtype virus (*10*, *11*).

Deployment of biological agents that spread in natural populations raises distinct regulatory considerations and may require a broad view of incentives for industrial investment (e.g., philanthropic benefits). When developed and applied carefully, self-spreading agents have benefitted human health (e.g., reduction of dengue using Wolbachia endosymbionts in mosquitoes (*13*)) and agriculture (e.g., control of plant pathogens using phage cocktails and baculoviruses (*14*)). The TVs we propose add complexity through their requirement for genetic modification. However, other self-spreading interventions harnessing genomic engineering (CRISPR, gene drives) are advancing, creating blueprints for how staged co-development can empower evidence-based policymaking and find solutions to regulatory, financial, and social challenges (*12*, *15*). Provided that a TV can be safely developed and shows promise for disease control, decisions on real world use would need to consider the balance of knowable harm done by withholding use and knowable harm done by release. The commitments presented here are intended to encourage deliberations characterized by understanding, accountability, and transparency, advancing a collaborative future in which TVs may contribute to the public good.

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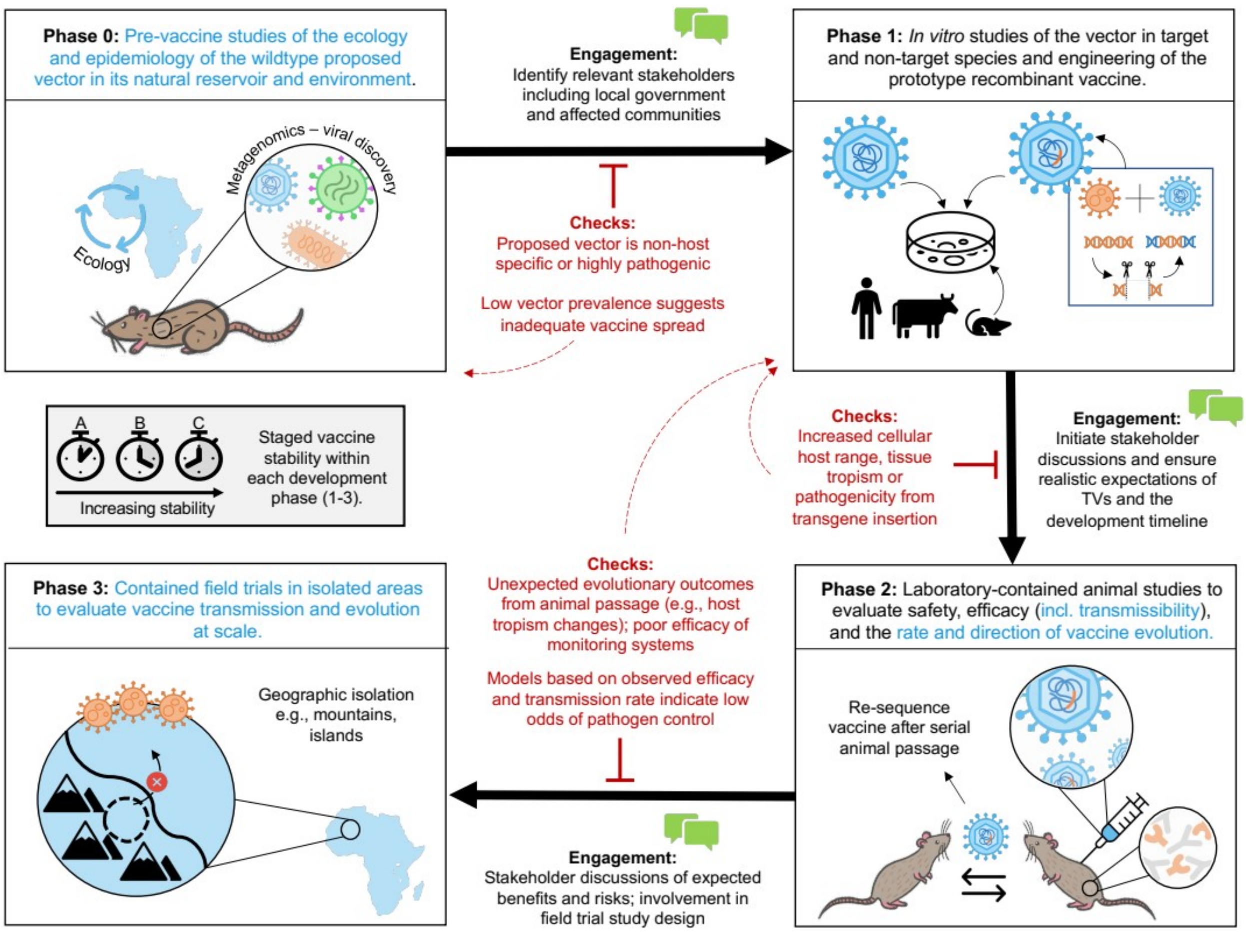

Figure 1. Transmissible vaccine development would proceed in discrete phases with established checkpoint criteria (red) necessitating vaccine re-design or an alternative viral vector. Stakeholder engagement (green dialog boxes), intersectorial meetings of scientists and regulators, and fundamental research into the evolution of replicating, engineered organisms encompass the full development process. Blue text indicates aspects that are distinct from conventional vaccine development.

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Box 1. **Seven proposed commitments for the responsible development of transmissible vaccines for infectious disease control in animals**

1. Vaccines will use naturally occurring, and host specific viruses as vectors, that would be isolated from and returned to their natural host species after antigen insertion.
2. Genetic modifications that increase host range, pathogenicity, or transmissibility, or create secondary hazards will not be intentionally pursued.
3. Technologies that could plausibly be harmful if applied to a human virus should be avoided.
4. Development will be staged with defined checkpoints and carried out within appropriately controlled environments.
5. Unintended spread and consequences will be monitored throughout development stages, with contingency plans.
6. Development will be transparent and community-led.
7. Safety standards will approach the strictest standards of partner nations involved.

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