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Developing Transmissible Vaccines for Animal Infections: Intrinsically Safe Designs and a Staged Transparent Development Process Will Be Essential

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POLICY FORUM

INFECTIOUS DISEASE

Developing transmissible vaccines for animal infections

Intrinsically safe designs and a staged transparent development process will be essential

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Many emerging and reemerging 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 the 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, which raises 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 codevelopment [see supplementary materials (SM)]—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 referred to as spillover). Diseases threatening wildlife health, either through recurrent spillover (e.g., Ebola in great apes) or after 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 using 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, from, 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. 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 of using an attenuated myxoma virus–based vaccine (*5*). Although no ill effects were reported before natural vaccine extinction, the myxoma virus used was not host specific and had only a brief coevolutionary 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 policy-makers, 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 cr[illegible] of TVs—we appraised the potential ecological and societal risks arising from transmission of an engineered viral vaccine (see SM). 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 will likely 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 for TVs would be 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.

Because vaccine safety hinges predominantly on the properties of the vector, we propose eligibility criteria. First, vaccines derived from cross-species transfer (e.g., the myxoma virus–based RHD vaccine) may spread unpredictably, causing ecological disruption. New selective environments, including the possibility of new coinfections with recombination-compatible viruses, might also promote evolution toward 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 (wild-type) or descendant (reversion to nonvaccine strain) viruses may inhibit vaccine spread, vectors that can infect hosts with prior or concurrent wild-type infections are desirable. Alternatively, competition with the wild type may be overcome by repeatedly introducing the vaccine or constructing it using locally rare or absent strains (*6*, *7*).

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, coevolutionary analyses supporting host-virus cospeciation over host switching, laboratory studies of cellular tropism, and animal inoculation studies. Ecologically plausible exposures in sympatric, nontarget 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

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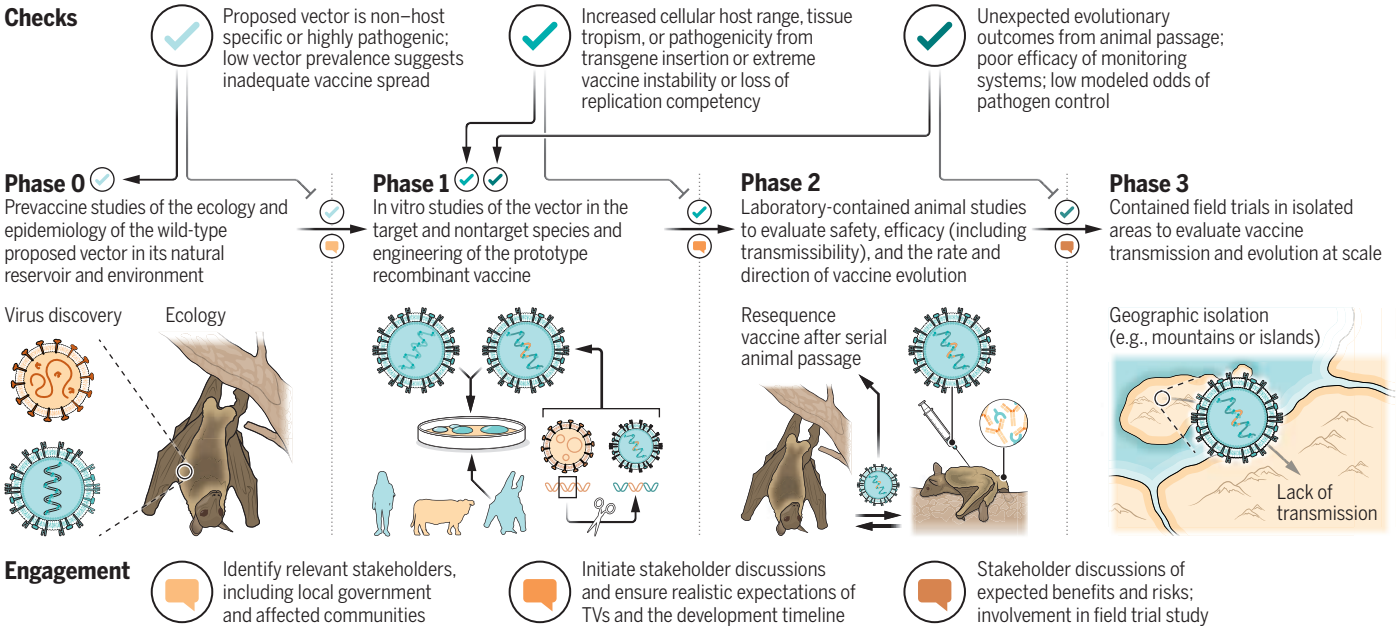
Phased development must incorporate checkpoints and engagement

Transmissible vaccine (TV) development would proceed in discrete phases, with established checkpoint criteria (✓) indicating continued development or necessitating vaccine redesign or an alternative viral vector. Stakeholder engagement (💬), intersectoral meetings of scientists and regulators, and fundamental research into the evolution of replicating, engineered organisms encompass the full development process. Phases 0 and 3 are distinct from traditional vaccine development, as are the focus on transmissibility and the rate and direction of vaccine evolution in phase 2.



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 because perturbing the coevolved virus-host equilibrium might select for a return to the undesirable ancestral state (see fig. S1). Unlike reversion of attenuated vaccines, reversion of TVs to their ancestral phenotypes creates no new 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 wild-type 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, the 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 previously unknown 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

The criteria described above should 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 either naturally isolated (e.g., islands or mountains) or experimentally isolated (e.g., enclosures or semifield systems) (see the figure). 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 continue 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 resequencing of the vaccine to monitor evolutionary changes and periodic in vitro monitoring of growth rate or cellular tropism. Because vaccinated animals have 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, or 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.

GRAPHIC: A. FISHER/*SCIENCE*

EQUITABLE PARTNERSHIPS WITH INTERNATIONAL GOVERNANCE

Although 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, nongovernment agencies, and affected communities (i.e., codevelopment). Initiating this process at project inception and certainly before the engineering of vaccine prototypes benefits vaccine developers by identifying technical and community values–based constraints that would alter deployment targets or development strategies (*12*). Communities affected by zoonotic spillover may desire rapid or geographically expanded TV deployment or, because of 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 the acceptance of conventional vaccines, thereby inadvertently harming health.

"...oversight as a shared, international responsibility underpins credibility..."

As with any vaccine, TV development will be subject to existing local, national, and international regulations for scientific research, production, and testing; to 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, whereas other stages (e.g., vaccine engineering and laboratory-contained animal trials) may be undertaken in countries with more funding and infrastructure. Because 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.

TOWARD 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, and Marburg virus) or where low-cost, scalable interventions could reduce pathogen threats to wildlife (e.g., WNS in bats, Ebola virus disease in nonhuman primates, and 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 wild-type 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 benefited 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 proposed here add complexity through their requirement for genetic modification. However, other self-spreading interventions harnessing genomic engineering (e.g., CRISPR and gene drives) are advancing, creating blueprints for how staged codevelopment can empower evidence-based policy-making 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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SUPPLEMENTARY MATERIALS

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Supplementary Materials for

Developing transmissible vaccines for animal infections

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Supplementary Text

Workshop organization

The workshop was held March 27 through March 31, 2023, in Stevenson Washington. Funding for the workshop was provided by a grant from the National Science Foundation (DEB 2216790). A core group of fourteen participants were invited by the organizers (Scott L. Nuismer and Daniel G. Streicker) and were selected to include diverse expertise, career stages, and published views on the merits of transmissible vaccines. After cementing the core participants, the workshop was advertised publicly through social media (e.g., Twitter), list-serves (e.g., evoldir, MIDAS), the workshop website (https://transmissiblevaccines.org/workshop-dev-vaccines/), and through the University of Idaho and University of Glasgow distribution networks. Seven additional participants were selected from the resulting applicant pool by the organizers based on a CV and one page description of research experience and interest in transmissible vaccines. All told, workshop participants represented five countries and were drawn from academia, government agencies, non-governmental organizations, and industry. Expenses associated with travel, lodging, and meals were paid for all workshop participants to remove financial barriers to participation. All participants were encouraged to present their research through an oral presentation and all participants engaged in structured discussions focused on resolving differences of opinion and achieving a consensus view. This Policy Forum represents the consensus viewpoint achieved during structured discussions that took place over the workshop and includes all workshop participants as authors.

Supplementary Box

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 environment
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

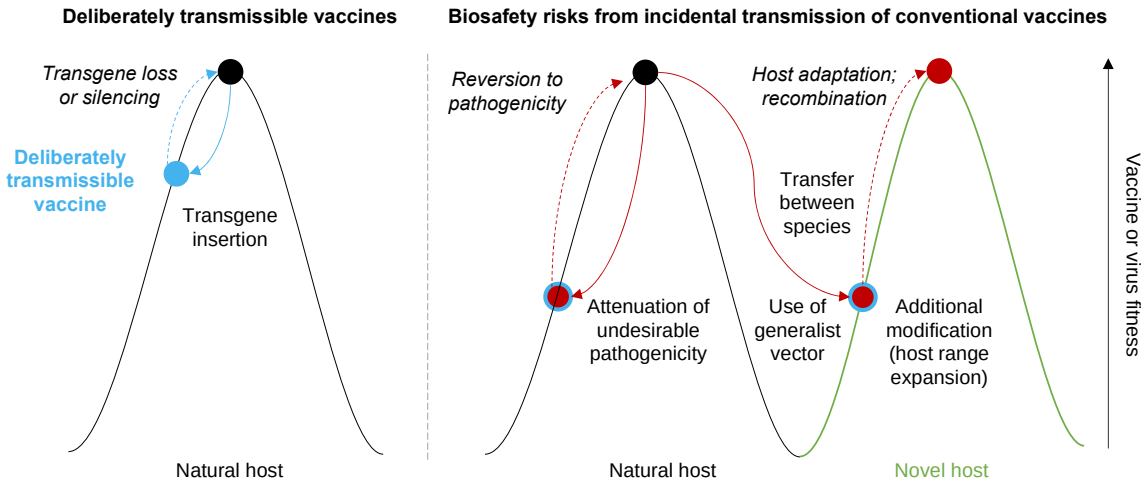

Fig. S1. Evolutionary outcomes of vaccine transmission depend on the viral vector and the genetic modifications introduced. Deliberately transmissible vaccines (left) are intended to minimally reduce and never increase viral fitness, which is already at its local, evolutionarily stable fitness peak due to co-evolution with an established host species. Fitness reduction is expected from transgene insertion. Using vaccines that behave as similarly as possible to their wildtype ancestors increases the likelihood that post-engineering evolution returns the vaccine to its current, pre-modification phenotype, whose sustained circulation would need to be acceptable to stakeholders. Alternative strategies (right), including attenuation by cross-species transfer or laboratory manipulation, risk evolution of novel phenotypes and are incompatible with our commitments. The depth and peaks of fitness valleys and the extent of fitness reduction will vary. Italicized text and dashed lines indicate evolutionary processes.