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SUPPLEMENT ARTICLE

First Do No Harm? Modeling Risks and Benefits of Challenge Trials for Hepatitis C Vaccine Development

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Background. In 2019, about 58 million individuals were chronically infected with hepatitis C virus. Some experts have proposed challenge trials for hepatitis C virus vaccine development.

Methods. We modeled incremental infections averted through a challenge approach, under varying assumptions regarding trial duration, number of candidates, and vaccine uptake. We computed the benefit-risk ratio of incremental benefits to risks for challenge versus traditional approaches. We also benchmarked against monetary costs of achieving incremental benefits through treatment.

Results. Our base case assumes 3 vaccine candidates, each with an 11% chance of success, corresponding to a 30% probability of successfully developing a vaccine. Given this probability, and assuming a 5-year difference in duration between challenge and traditional trials, a challenge approach would avert an expected 185 000 incremental infections with 20% steady-state uptake compared to a traditional approach and 832 000 with 90% uptake (quality-adjusted life-year benefit-risk ratio, 72 000 & 323 000). It would cost at least $92 million and $416 million, respectively, to obtain equivalent benefits through treatment. BRRs vary considerably across scenarios, depending on input assumptions.

Conclusions. Benefits of a challenge approach increase with more vaccine candidates, faster challenge trials, and greater uptake.

Keywords. hepatitis C; vaccines; challenge trials; DALYs.

Hepatitis C virus (HCV) is a growing cause of global disease and death, with an estimated 542 000 deaths, 15.3 million disability-adjusted life years (DALY), and 1.5 million new chronic infections in 2019 [1, 2]. About 80% of the HCV burden occurs in low- and middle-income countries (LMICs) [3]. In 2017, buoyed by the development of direct-acting antiviral (DAA) therapies with high cure rates and minimal side effects, the World Health Organization set a goal of eliminating HCV by 2030 [4]. However, there remain substantial impediments to elimination, as only 20% of HCV cases are diagnosed, 15% of diagnosed individuals receive treatment, and treated individuals remain susceptible to reinfection [5–7]. In light of these barriers, an HCV vaccine that prevents chronic infection would be an important element of elimination strategies.

Vaccine development for HCV has proven difficult [8]. Because traditional HCV vaccine trials require long follow-up and DAAs can treat infection [9], some experts have proposed a controlled human infection model ("challenge trials") for HCV vaccine candidates [10]. In challenge trials, participants are deliberately exposed to a pathogen after receiving a vaccine candidate or placebo. This allows for faster trials but increases risks to participants. Ethicists broadly agree that challenge trials may meet the Belmont Report standard that "risks to subjects be outweighed by…anticipated benefit to society" [11]. However, each application requires assessment of context-specific risks to research subjects and expected trial benefits.

In this article, we model the risks and benefits of challenge trials for HCV vaccine development. With considerable uncertainty around parameters, our objective is not to produce precise, definitive estimates. Rather, we start from the premise that debates about HCV challenge trials invoke assumptions about the magnitude of risks and benefits but that such assumptions are seldom explicit. Through this exercise, we develop a framework that elucidates key input parameters and value judgments required for assessing challenge trials [12]. We then provide a range of estimates of the benefit-risk tradeoff for HCV vaccine development.

METHODS

Benefits

We define the benefit of a hypothetical HCV vaccine in reference to the present value of all future infections averted. The incremental benefit of a challenge approach is the increase in

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future infections averted through faster vaccine development, beyond those prevented with a traditional approach. We modeled expected incremental future infections averted, discounted to present value, as the product of (1) reduction in time to vaccine availability afforded by a challenge versus traditional approach, (2) vaccine uptake, (3) efficacy, and (4) projected chronic HCV incidence (Supplementary Figure 1).

Reduction in Time to Vaccine Availability

In a challenge approach, we assumed that challenge trials would replace either traditional Phase 1/2 trials (after Phase Ia safety testing) or Phase 2 trials. Each challenge trial would be shorter than a traditional trial by some number of years (y), speeding development and increasing expected benefit. After a promising candidate is identified, traditional Phase 2/3 or 3 trials would be conducted in either approach. Therefore, after challenge trials are complete, we assumed that the pathway to and timeline for drug approval would be the same for both challenge and traditional approaches. (See Supplementary Methods 1 for discussion of alternative trial pathways.)

We further assumed there is some number of candidate vaccines eligible for challenge trials (T), each with a constant probability of success (p) of identifying a successful vaccine. While, in practice, candidates have different probabilities of success, this assumes a threshold probability below which researchers would not attempt a trial, and, given this threshold, provides a lower bound on expected years saved.

We assumed that researchers conduct sequential trials, each with probability of success p, until either a trial identifies an effective vaccine or T trials are completed without a successful candidate identified. (See assumption discussion in Supplementary Methods 1.) In our base case estimate of years saved by a challenge approach, we count benefits only if a successful candidate is identified. For example, if the first candidate is successful, a challenge approach reduces time to vaccine by y years; if the second is successful, the approach shortens it by $2y$ years (Supplementary Equation 1). In sensitivity analysis, failures could save up to 10 years in future research (Supplementary Equation 2).

We varied the success probability (p) from 1% to 40% (base case, 11%; the proportion of vaccines with a Phase 2 trial which go on to reach vaccine approval) [13], the difference in trial length (y) from 2.5 to 10 years (base case, 5 years; from a prior HCV vaccine trial) [9], and the number of candidates (T) from 1 to 5 (base case, 3) (Table 1). We set the years until benefits accrue (R) to 30, allotting time for post-challenge trial development, vaccine rollout, and delay from vaccination to averted infection. We discounted at 3% per year in the base case, following common practice in health economics.

Vaccine Deployment

We varied global vaccine deployment (v) between 5% and 90% in reference to other vaccines against human papillomavirus (14%), rotavirus (23%), hepatitis B virus (90%) (Supplementary Tables 1 and 2 and Supplementary Methods 2). To capture total incremental benefit over a traditional approach, uptake estimates reflect "steady-state" coverage, after initial scale-up (Supplementary Methods 3). We assumed homogeneous coverage of the population with respect to risk; if instead, for example, the vaccine were provided only to members of high-risk groups, this parameter should reflect risk-weighted uptake.

Vaccine Efficacy and Waning

We varied vaccine efficacy (e) between 50% and 90%, with a base case of 70% reflecting either a moderately protective vaccine or a highly protective vaccine with waning [20, 21].

Projected HCV Incidence

We used projections of future HCV annual incidence (i) in the absence of a vaccine from a previously published model, which simulated 2016–2090 incidence as a function of past prevalence, demography, injection drug usage, and prevention and treatment programs [16, 17]. As a base case, we used incidence estimates for 2055 to allow time for vaccine development, rollout, and aging into infection. We also performed sensitivity analysis in which projected incidence was halved from the base case, representing scale-up of prevention and treatment.

We obtained the total expected benefit (E(B)), the present value of incremental infections averted through a challenge approach, by multiplying as follows:

$$E(B) = v\,e\,i\,E(Y).$$

The term $E(Y)$, which represents expected reduction in time to vaccine availability as a function of success probability (p), number of candidates (T), and difference in length between traditional and challenge trials (y), was formulated to capture discounting of future effects to present value (Supplementary Equation 1).

Risks

We modeled incremental expected risk to participants, $E(R)$, in terms of HCV infections incurred during challenge trials, assuming 100 participants per challenge trial, equally sized treatment and placebo arms, and 0% efficacy in failed vaccine candidates (Supplementary Equation 3). Because challenge trial participants are likely to be healthy and otherwise at low risk of contracting hepatitis C, we treat all trial-incurred infections as incremental to those incurred in the course of traditional vaccine development.

Risk-Benefit Weighting

We summarize benefits and risks drawing on 3 types of ethical considerations outlined in prior literature (Supplementary Table 3) [22–25]. We first considered risks to participants,

Table 1. Model Parameters

Parameter	Description	Value (Range)	Source
Years saved by challenge trial approach			
Probability of success of each trial (*p*)	As the base case, we used the probability of approval of non–industry-sponsored Phase 2 vaccine candidates: 11%. To reflect Phase 1 candidates (eg, a combined Phase 1/2 trial as in reference [9]) or a lower probability of success given a more challenging target, we also present results with this parameter set at 7%.	11% (7%, for Phase 1 to approval, up to 40%; presented in the Supplementary Figures S2 and S3)	[13]
Difference in duration (in years) between a traditional and challenge trial (*y*)	The Phase 1/2 trial described in reference [9] lasted 6 years. Our base case estimate assumed that a challenge trial could be conducted in a year. The lower bound estimate assumed additional regulatory requirements for a challenge trial increasing duration; the upper bound assumed more interest in research (and, eg, simultaneous trials) when faster trials are possible.	5 (2.5–10)	[9]
No. of vaccine candidates eligible for challenge trials (*T*)	This parameter reflects the number of vaccine candidates on which researchers are willing to conduct challenge trials. We set the base case number of candidates at 3.	3 (1–5)	Assumed
Years until benefits accrue (*R*)	For a successful vaccine, we assumed 5–10 years of additional development including a Phase 3 trial, 5–10 years of scale-up, and 10–15 years from vaccination to averted infection.	30	[14, 15]
Deployment			
Vaccine uptake	We modeled vaccine uptake based on comparable vaccines (HBV, rotavirus, HPV).	Varied (5%–90%)	See Supplementary Table 2
Vaccine efficacy/waning			
Vaccine efficacy	We assumed that vaccines at <50% efficacy would not be approved. Because an HCV vaccine has been challenging to develop, experts anticipate a moderate efficacy and/or waning.	70% (50%–90%)	Assumed
Projected HCV infections			
HCV incidence rate (no vaccine scenario)	We used estimates of global HCV incidence from a previously published model ("status quo" specification for 2055). (Because projected incidence was fairly stable around this horizon, we applied this point estimate over all years of estimated benefit.)	0.02/100 (Sensitivity analysis, 0.01/100)	[16]
Population	We used World Bank population projections for 2055.	9.67 billion	[17]
Adjustment factor	We adjusted projected incidence based on the ratio of retrospectively-estimated incidence by the World Health Organization to projected incidence for 2019 [2] (Supplementary Methods 4).	0.7	[2, 16]
Risks			
Sample size	Challenge trials usually include 10–100 participants; we used the upper end of this range assuming that a larger trial is needed for regulatory approval, compared to other trial purposes.	100	[18, 19]

Abbreviations: HCV, hepatitis C virus; HPV, human papillomavirus.

estimating a low average participant health impact of 0.02 quality-adjusted life-years (QALYs) from acute hepatitis C, with minimal risk of long-term complications (Supplementary Table 4) [23]. We therefore assumed that long-term health harms would be sufficiently controlled with high-efficacy, short-duration DAAs, such that a challenge trial may be appropriate depending on the magnitude of incremental benefits and the costs of obtaining benefits through other strategies [26].

If risks fall within a potentially acceptable range, a second consideration is whether expected benefits outweigh expected risks. Even when severe health risks are well controlled, challenge trials incur extra infections, participant discomfort, and some risk of severe health outcomes, and expected benefits must outweigh these extra health losses. Beyond discounting, ethicists suggest potentially upweighting risks to participants to reflect uncertainty (ie, that incremental future benefits are obtained with fairly low probability) and other ethical considerations (ie, protection of subjects, commission vs omission, risks of distrust in the research process) [17, 18].

To inform this consideration, we first present the benefit-risk ratio (BRR)–$[E(B)]/[E(R)]$—future expected incremental infections averted in a challenge approach compared to a traditional approach, divided by incremental infections incurred in a challenge approach [27]. We then convert this ratio to QALYs to capture the difference in expected health effects for non-trial and trial infections. To convert to QALYs, we use a conversion factor of 100, based on a 33% future non-trial treatment rate, an average loss of 3 QALYs per untreated (non-trial) chronic infection, and an average of 0.02 QALYs lost per treated trial infection (Supplementary Table 4).

Third, we considered the cost of obtaining similar benefits through alternative means: benchmarking challenge approach benefits against the minimum cost of obtaining equivalent incremental benefits for patients with hepatitis C through treatment [28]. We quantified the cost of treating the expected number of future present-valued infections prevented by a vaccine, assuming a $500 cost for detecting and treating an early-stage HCV infection in LMICs (Supplementary Table 5). This provides a conservative estimated monetary value of a challenge model, omitting differences in trial costs (discussion in Supplementary Methods 5).

Analyses were conducted using R software, version 4.0.2. Model code and an interactive Shiny app are publicly available.

RESULTS

The probability of identifying a successful vaccine given 3 independent candidates was 30% with a per-trial success probability of 11% and 20% with a per-trial success probability of 7% (Supplementary Equation 4 and Supplementary Figure 2). These increased to 44% and 30%, respectively, with 5 candidates. Expected years saved by a challenge approach were higher when there were more vaccine candidates available, a larger difference in duration between challenge and traditional trials, and higher per-trial success probabilities (Supplementary Figure 3).

In Figure 1, we present expected incremental future infections averted across different scenarios, discounted to present value. With a base case per-trial success probability of 11%, 5-year difference in trial length, and 3 vaccine candidates, we estimated an expected 185 000 incremental infections averted with 20% vaccine uptake and up to 832 000 infections averted with 90% uptake. With a 7% per-trial success probability, these estimates declined to 124 000 and 559 000, respectively. Increasing the number of vaccine candidates had a superlinear effect; with a 11% success probability, a challenge approach with a single candidate would avert 39 000 incremental infections on expectation with 20% uptake, while 5 candidates would avert 367 000. Expected incremental infections incurred from a challenge approach depended primarily on the number of available candidates and increased with this parameter (eg, from 96 with 1 candidate to 386 with 5 candidates at a 11% per-trial success probability).

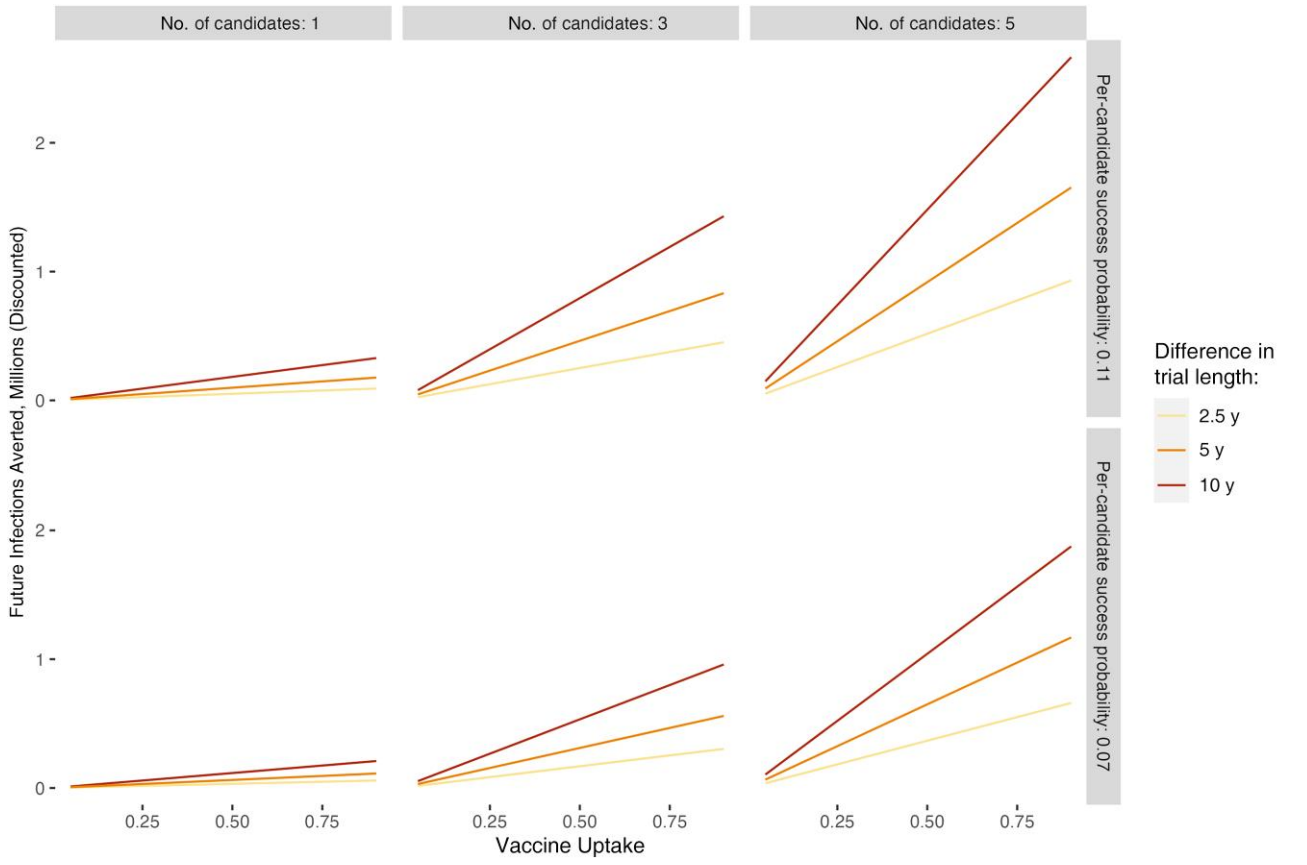

Figure 1. Incremental future infections averted (discounted). The x-axis displays vaccine uptake. The y-axis displays future infections averted (millions, discounted to present value). We vary the number of vaccine candidates across columns and per-trial success probability across rows. Colors correspond to the difference in duration between each traditional and challenge trial. y, years.

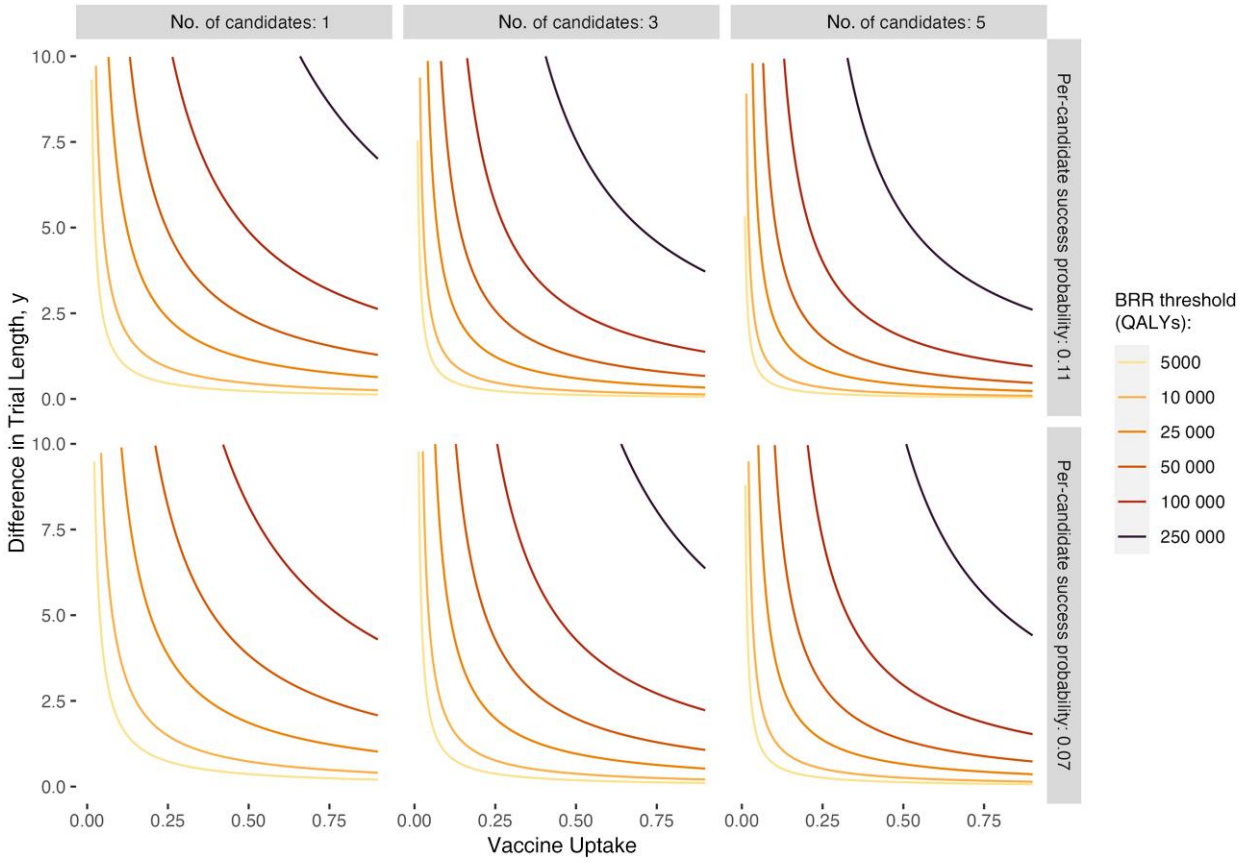

Figure 2. Quality-adjusted life-year (QALY) benefit-risk ratio (BRR) frontiers across different parameter values. Each line shows the frontier for the color-corresponding QALY BRR, which is defined as the expected incremental future QALYs gained by a challenge trial (benefits), discounted to present value, divided by incremental additional QALYs lost by a challenge trial (risks). In other words, all points above a line have a BRR above that indicated by the line. We vary global vaccine uptake across the x-axis and the difference in trial length between each traditional and challenge trial on the y-axis. The number of available vaccine candidates is varied across columns, and the per-trial success probability is varied across rows. Infection BRRs and sensitivity analyses are presented in the Supplementary Materials (Supplementary Figures 4 and 6–9).

We next quantify BRRs, the incremental benefits divided by incremental risks, where higher BRRs are more favorable. For our base case, we found an infection BRR of 720 with 20% uptake and 3200 with 90% uptake, indicating that a challenge approach would be preferable if averting 700 or 3200 future discounted infections were a sufficient trade-off for each incremental treated infection incurred in challenge trials. Converted to a QALY scale, these BRRs were 72 000 and 320 000, respectively (Figure 2). Based on costs of detection and treatment in LMICs, we estimated the monetary value of these health benefits at $92 and $416 million ($360 000 and $1.6 million per trial infection) (Supplementary Figure 5).

BRRs and monetary value decreased with a 7% per-trial success probability (corresponding QALY BRRs, 46 000 and 210 000). For scenarios in Figure 1, there was a wide range of BRRs (QALYs, 3300–690 000), with a QALY BRR interquartile range of 52 000–200 000 (68 000–250 000 at 11% per-trial success probability and 43 000–160 000 at 7%).

For sensitivity analyses (Supplementary Figures 6–9), we provide BRRs under alternative scenarios, including 90% vaccine efficacy, a 50% reduction in global incidence, "generous" estimates of years saved, and no discounting. The first 2 had linear impacts on estimated BRRs (1.3 and 0.5, respectively). Discounting yielded BRRs lower by a median factor of 0.4. Generous estimates of "years saved" yielded higher BRRs, but the increase was driven by benefits in the case where no vaccine is developed, rendering estimates of averted infections less interpretable.

DISCUSSION

Our results provide a framework for explicitly examining the potential impact of challenge trials for an HCV vaccine. We find that a challenge approach would have the largest benefit when there are multiple vaccine candidates and researchers are willing to conduct repeated challenge trials after failed candidates. Given low success probabilities of vaccine trials, a

single challenge trial remains unlikely to identify an effective vaccine and offers less benefit over a traditional approach than a strategy of multiple trials.

The difference in duration between traditional and challenge trials also strongly affects potential benefits. This underscores the importance of strong regulatory and logistical infrastructure. If challenge trials are highly cumbersome to approve, they may be similar in length to traditional trials, reducing benefits of shorter duration. However, if they can be efficiently planned and executed, they may offer significant time savings over traditional trials, which can be impactful for high-incidence diseases like HCV.

We estimate the value of a challenge approach in terms of both BRRs and monetary costs. Our results provide a rough range of likely BRRs: nearly all scenarios corresponding to Figure 1 had an infection BRR of ≥50 (QALY BRR, 5000) while <20% exceeded 2500 (QALY, 250 000). Of scenarios with global steady state uptake ≥50%, 80% had an infection BRR >1000 (QALY, 100 000). This BRR threshold would imply a value per challenge infection of ≥$500 000, but this monetary benchmark is conservative. In particular, we do not account for reduced trial costs in a challenge approach, as the appropriateness of using challenge trials specifically to reduce research costs remains an issue of ethical debate [22]. However, for HCV, traditional trials may be uniquely difficult to accomplish owing to limited institutions with experience doing research in high-risk populations, making both financial and non-financial costs potentially salient.

Although there is substantial uncertainty about numerical results, our approach allows us to categorize uncertainty into 3 types: knowable and/or policy-driven (eg, trial length, number of candidates, and vaccine uptake), unknown (eg, vaccine efficacy, trial success probability, and future changes in disease incidence), and value defined (eg, discount rate and minimum BRR threshold). In particular, while many unknowable quantities affect the potential value of challenge trials, researchers and policymakers can increase confidence that the likely BRR exceeds a minimum threshold by optimizing factors under their control: focusing on high-burden diseases, minimizing trial length and supporting broad vaccine deployment. The last has the potential to have particularly significant impact: vaccine uptake affects BRR multiplicatively, and uptake for comparable vaccines ranges from 20% (human papillomavirus/rotavirus) to nearly 90% (hepatitis B virus). To facilitate high uptake, policymakers may consider introducing a hepatitis C vaccine in the infant schedule if feasible; coverage has historically lagged for vaccines targeted to older ages and even more for those targeted to high-risk groups [29–31]. They might also coordinate financing efforts early to ensure accessibility in LMICs.

Our framework also invites readers to debate value judgments embedded in decisions about challenge trials, notably how to discount future benefits and the appropriate threshold for the BRR. In this article, we use a 3% discount rate, common in health economics, which yields present value benefit estimates that are around 40% of undiscounted benefits. The appropriate discount rate for costs and benefits, however, remains a topic of debate [32]. Readers may also disagree on BRR thresholds. Some may argue for a lower threshold, based on the logic that infections incurred in a trial receive effective treatment. Others may advocate for a higher threshold based on the uncertainty of identifying an effective vaccine and concern about perceptions of integrity in the research process. To allow readers to explore different beliefs and assumptions, we provide an online interactive version of our model.

There are additional limitations to our study. Our model simplifies the research process and does not consider complex counterfactuals. For example, challenge trials could perhaps catalyze research that would otherwise not occur, which would have greater benefits than explored here. However, we believe that our approximation is appropriate, given that other approaches could incentivize traditional trials if time differences were insignificant. Furthermore, because of limited data, we make simplifications (eg, assuming a constant "floor" success probability of each vaccine trial) that would benefit from additional context-specific data, and there are significant uncertainties around future incidence and treatment. Nevertheless, our estimates suggest, despite conservative assumptions, that benefits of a challenge approach are potentially significant relative to risks and that policies focused on streamlining the regulatory process and ensuring that vaccines are widely available once approved can maximize potential benefits.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Acknowledgments. Data and code are publicly available on GitHub: https://github.com/abilinski/HepC_Challenge. An interactive version of the model is also available at https://rachel-slimovitch.shinyapps.io/3_app/.

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