**First Do No Harm? Modeling risks and benefits of challenge trials for hepatitis C vaccine development**

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### Abstract

In 2019, about 58 million individuals were chronically infected with hepatitis C virus (HCV). Some experts have proposed challenge trials for HCV vaccine development. 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 (BRR) of incremental benefits to risks for challenge versus traditional approaches. We also benchmarked against monetary costs of achieving incremental benefits through treatment. With 3 vaccine candidates and a 5-year difference in duration between challenge and traditional trials, a challenge approach would avert on average 185,000 incremental infections with 20% steady-state uptake and 832,000 with 90% uptake (QALY BRR: 72,000-320,000). It would cost at least $93 million and $416 million, respectively, to obtain benefits through treatment. Under conservative assumptions, benefits of a challenge approach may be significant relative to risks; these increase with more candidates, faster trials, and greater uptake.

Hepatitis C virus (HCV) is a growing cause of global morbidity and mortality, with approximately 542,000 deaths, 15.3 million DALYs, and 1.5 million new chronic infections in 2019 [[1]](https://www.zotero.org/google-docs/?Meqty2). About 80% of HCV burden occurs in low- and middle-income countries (LMIC) [[2]](https://www.zotero.org/google-docs/?CDNifo). In 2017, buoyed by the development of direct-acting antiviral therapies (DAAs) which have high cure rates and minimal side effects, the World Health Organization set a goal of eliminating HCV by 2030 [[3]](https://www.zotero.org/google-docs/?qa3e19). However, there remain substantial impediments to elimination, as only 20% of individuals with HCV are diagnosed, 15% of diagnosed individuals receive treatment [[4]](https://www.zotero.org/google-docs/?4CCHmo), and treated individuals remain susceptible to reinfection [[5,6]](https://www.zotero.org/google-docs/?mrQbk3). 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 [[7]](https://www.zotero.org/google-docs/?d1ajJl). Because traditional HCV vaccine trials require long follow-up and DAAs can treat infection [[8]](https://www.zotero.org/google-docs/?9L0cFc), some experts have proposed a controlled human infection model (“challenge trials”) for HCV vaccine candidates [[9]](https://www.zotero.org/google-docs/?OYZTqA). In challenge trials, participants are deliberately exposed to a pathogen after receiving a vaccine candidate or placebo. This allows for faster trials, but increases risk 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” [[10]](https://www.zotero.org/google-docs/?tWm48G). However, each application requires assessment of context-specific risks to research subjects and expected benefits.

In this paper, we model 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 critical parameters affecting the magnitude of benefits and risks as well as key value judgments required for assessing challenge trials [[11]](https://www.zotero.org/google-docs/?FfMdl7). We then provide a range of estimates of the benefit-risk tradeoff for HCV vaccine development.

### Methods

#### Benefits

We defined benefits of an HCV vaccine in reference to the present value of the full stream of future infections averted through a vaccine. The incremental benefit of a challenge approach is the increase in future infections averted beyond those prevented by a traditional approach. We modeled 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 (Figure S1).

#### Reduction in time to vaccine availability

In a challenge approach, we assumed that challenge trials would replace traditional Phase 1/2 or 2 trials and that each challenge trial would be shorter than a traditional trial by some number of years (*y*). After a promising candidate is identified, a traditional Phase 2/3 or 3 trial would be conducted in either approach. Therefore, after Phase 1/2 or Phase 2 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.

We further assumed sufficient candidate vaccines to attempt a maximum number of trials (*T*), each with a 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 discussion of this assumption in Methods S1.) In our base case estimate of years saved by a challenge approach, we only count benefits 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 2*y* years (Equation S1). In sensitivity analysis, we allowed failures to save up to 10 years in future research (Equation S2).

We varied *p* from 1% to 40% (base case: 11%, parameterized as probability of vaccine approval given a phase 2 trial) [[12]](https://www.zotero.org/google-docs/?6eaXiR), *y* from 2.5 to 10 (base case: 5, based on a prior HCV vaccine trial) [[8]](https://www.zotero.org/google-docs/?Sqt5ej), and *T* from 1 to 5 (base case: 3) (Table S1). We set *R* to 30, allotting time for post-trial development, vaccine roll-out, 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 10% and 90%, defined in reference to comparable vaccines: human papillomavirus (HPV) (14%), rotavirus (23%), hepatitis B virus (HBV) (90%) (Table S2-3, Methods S2). To capture total incremental benefit over a traditional approach, these estimates reflect “steady-state” uptake, after initial scale-up (Methods S3).

#### 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 [[13,14]](https://www.zotero.org/google-docs/?1HnMRC).

#### Projected HCV incidence

We used projections of HCV incidence (*i*) from a previously published model, which simulated 2020-2090 incidence as a function of past prevalence, demography, injection drug usage, and prevention and treatment programs [[15]](https://www.zotero.org/google-docs/?jVh9Z8) and World Bank population projections [[16]](https://www.zotero.org/google-docs/?yOiU73). As a base case, we used “status quo” incidence estimates for 2055 to allow time for vaccine development, roll-out, and aging into infection; we also performed sensitivity analysis in which incidence was halved from base case, representing scale-up of prevention and treatment.

We obtained the present value of incremental infections averted through a challenge approach by multiplying:

The term *E(Y),* which represents expected reduction in time to vaccine availability, was formulated to capture discounting of future effects to present value (Equation S1).

#### Risks

We modeled the risk to participants in terms of hepatitis C infections, assuming 100 participants per challenge trial (*n*), equally sized treatment and placebo arms, and 0% efficacy in failed vaccine candidates. We estimated expected incremental infections *E(R)* per Equation S3.

#### Risk-Benefit Weighting

We summarize risk and benefits drawing on 3 types of ethical considerations outlined in prior literature (Table S4) [[17–20]](https://www.zotero.org/google-docs/?X1cvEm). We first consider risks to participants, comparing trial risks to those incurred in daily activities and in other medical procedures. We estimated a low average participant cost of 0.02 QALYs from acute hepatitis C, with minimal risk of long-term complications (Table S5) [[18]](https://www.zotero.org/google-docs/?jy2QND). 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 [[21]](https://www.zotero.org/google-docs/?gHMZC3).

If risks fall within a generally-accepted range, a second consideration is whether expected benefits merit expected risks. Beyond discounting, ethicists suggest potentially upweighting risks to participants to reflect uncertainty (i.e. that incremental future benefits are obtained with fairly low probability) and other ethical considerations (i.e, protection of subjects, commission vs. omission, risks of distrust in the research process). We first present the benefit-risk ratio (BRR) of future infections averted by a vaccine to treated infections in participants across different scenarios [[22]](https://www.zotero.org/google-docs/?yINwzA). We then convert this ratio to quality-adjusted life-years (QALYs), to capture the difference in expected health costs for non-trial and trial infections. We assumed that future untreated infections cost 4 QALYs on average (Table S5), a 50% future treatment rate, and that treated trial infections cost 0.02 QALYs, for a conversion factor of 100.

Third, we consider the cost of obtaining similar benefits through alternative means: benchmarking challenge approach benefits against the minimum cost of obtaining equivalent incremental benefits for hepatitis C patients through treatment [[23]](https://www.zotero.org/google-docs/?A1Zlxr). We quantify the present value cost of treating the expected number of future infections prevented by a vaccine, assuming a $500 cost for detecting and treating an early stage hepatitis C infection in LMIC (Table S6). This provides a conservative estimated monetary value of a challenge model, omitting differences in trial costs (discussion in Methods S4).

Analyses were conducted in R v4.0.2. Model code and an interactive Shiny app are publicly available.

### Results

The probability of identifying a successful vaccine given 3 candidates is 30% with a per-trial success probability of 11% and 17% with a per-trial success probability of 6% (Equation S4, Figure S2). These increase to 44% and 27% respectively with 5 candidates. Expected years saved by a challenge approach are higher when there are more vaccine candidates available, a larger difference in duration between challenge and traditional trials, and higher per-trial success probabilities (Figure S3).

In Figure 1, we present expected incremental future infections averted across different scenarios. With a base case per-trial success probability of 11%, 5-year difference in trial length, and 3 vaccine candidates, we estimated 185,000 incremental infections averted with 20% vaccine uptake, up to 832,000 infections averted with 90% uptake. With a 6% per-trial success probability, these estimates were nearly halved: 108,000 to 486,000. 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 infections incurred by a challenge trial depended primarily on the number of available candidates and increased roughly linearly with this parameter (e.g., from 98 with 1 candidate to 386 with 5 candidates at a 11% per-trial success probability).

In Figure 2, we show BRRs across different scenarios, where higher BRRs are more favorable. For our base case, we found an infection BRR of 700 with 20% uptake and 3200 with 90% uptake, which indicates that a challenge approach would be preferable if averting 700 or 3200 infections is a sufficient trade-off for each treated infection incurred in challenge trials. On the QALY scale, BRRs were 72,000 and 320,000, respectively (Figure S4); based on costs of detection and treatment in LMIC, we estimated the monetary value of these scenarios at $93 million and $416 million ($350,000 and $1.6 million per infection) (Figure S5).

As with expected future infections averted, BRRs and monetary value were nearly halved with a 6% per-trial success probability, to 400 and 1800 for infections. For scenarios in Figure 2, there was a wide range of BRRs (infections: 15-9000), with an infection BRR interquartile range of 300-1300 (400-1700 at 11% per-trial success probability and 200-900 at 6%).

For sensitivity analyses (Figures S6-S9), 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 two have linear impacts on estimated BRRs (1.3 and 0.5, respectively). Discounting yields BRRs lower by a factor of about 0.4. Generous estimates of “years saved” yielded higher BRRs by a median factor of 8, with the increase 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 understanding 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 rates 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 each traditional and challenge trial also strongly affects potential benefits. This too underscores the importance of a 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 particularly impactful for high-incidence diseases like HCV.

We estimate the value of a challenge approach in terms of both benefit-risk ratios and monetary costs. Our results provide a rough range of likely BRRs: nearly all scenarios that we explored had an infection BRR of at least 50 (QALY: 5000) while relatively few exceeded 2,500 (QALY: 250,000). To obtain an infection BRR ratio over 1,000 (QALY: 100,000) with a 5-year difference in trial length, many scenarios required global steady-state vaccine uptake of at least 50%. This threshold implies a value per challenge infection of at least $500,000, but this monetary benchmark is conservative. In particular, we do not factor in 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 [[17]](https://www.zotero.org/google-docs/?uRMPwS). However, for HCV, traditional trials may be uniquely difficult to accomplish due 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 three types: knowable and/or policy-driven (e.g., trial length, number of candidates, vaccine uptake), unknown (e.g., vaccine efficacy, trial success probability, future changes in disease incidence), and value-driven (e.g., discount rate, 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 vaccine deployment plans. The last has the potential to be particularly impactful: vaccine uptake affects the BRR multiplicatively, and uptake for comparable vaccines ranges from 20% (HPV/rotavirus) to nearly 90% (HBV). To facilitate high uptake, policymakers may consider introducing a hepatitis C vaccine in the infant schedule, as coverage typically lags for vaccines targeted to older ages, and might also coordinate financing efforts early to ensure accessibility in low- and middle-income countries [[24]](https://www.zotero.org/google-docs/?7OJA7M). By contrast, attempting to target vaccination solely to high risk populations may curtail health benefits.

Our framework also invites readers to debate value judgements 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, commonly 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 [[25]](https://www.zotero.org/google-docs/?UYVVPa). 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 remain additional limitations of 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 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 (e.g., 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 vaccine availability once approved can maximize potential benefits.

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Data and code will be made publicly available on GitHub.

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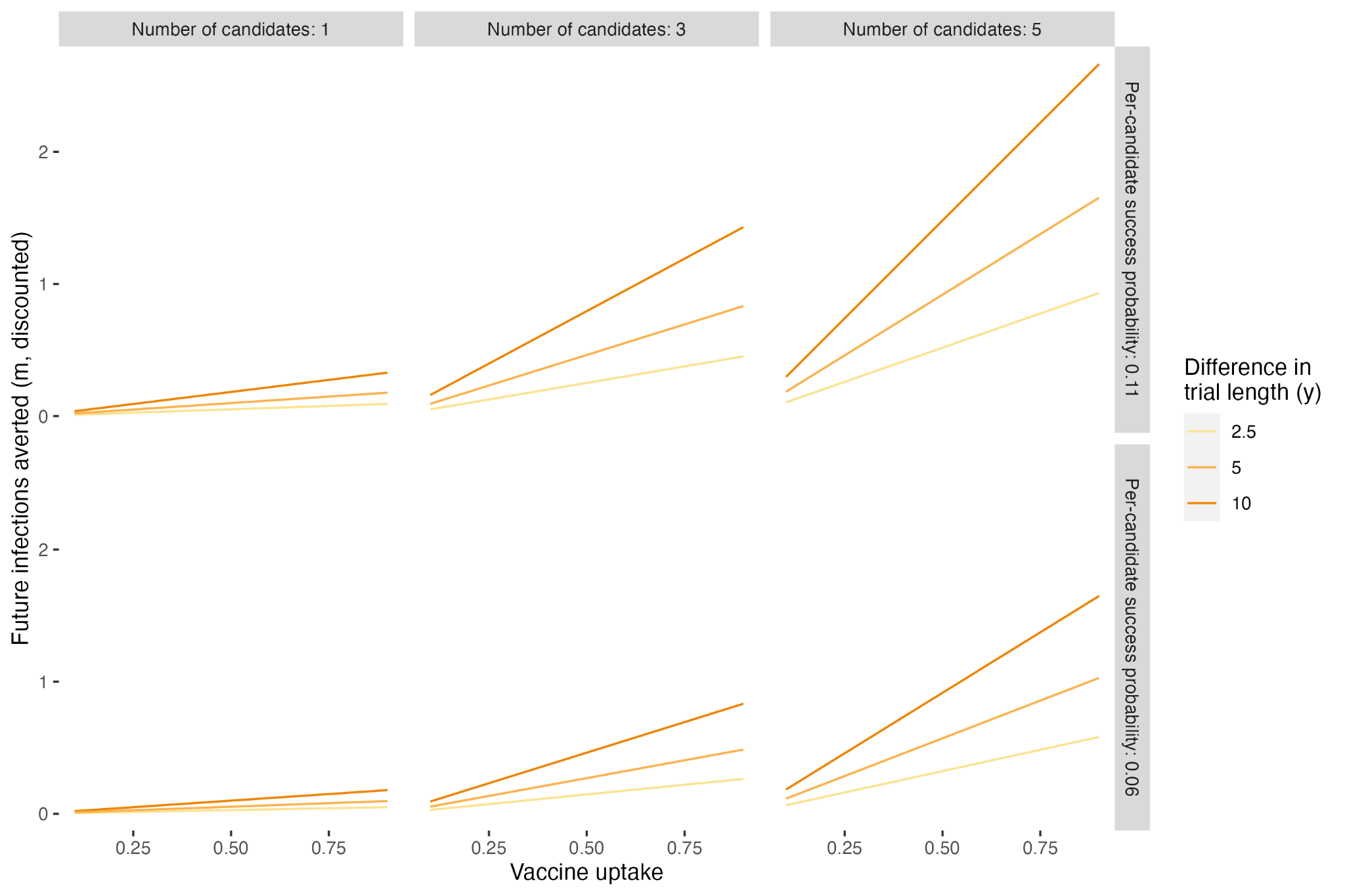
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### Figures

**Figure 1. Incremental future infections averted (discounted).** The x-axis displays vaccine uptake and 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 length (years) between a traditional and challenge trial.

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**Figure 2. Infection benefit-risk frontiers across different parameter values.** Each line shows frontier for a given level of the infection benefit-risk ratio (BRR): expected incremental future infections averted by a challenge trial, discounted to present value (benefits) vs. incremental additional infections incurred 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 (years) 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. QALY BRRs and sensitivity analyses are presented in the Supplement (Figures S4, S6-9).