Optimal portfolios of blood safety interventions: test, defer or modify?

#### Blinded submission

# Abstract

**Background** In most health systems, risk of transfusion-transmissible infections (TTIs) is managed through a portfolio of blood safety interventions. Shifting epidemiological conditions, emerging infectious diseases, and new technologies necessitate periodic reassessment of blood safety portfolios. However, the number of available blood safety portfolios grows exponentially with the number of available interventions, making it impossible for policy makers to evaluate all feasible portfolios without the assistance of a computer model.

**Methods** We developed a novel optimization model for evaluating blood safety portfolios that enables systematic comparison of all feasible portfolios of deferral, testing, and modification interventions to identify the portfolio that is preferred from a cost-utility perspective. We developed methods to efficiently solve this binary integer program. We applied the method to retrospectively evaluate U.S. blood safety policies for Zika and West Nile virus for the years 2017, 2018, and 2019, defining donor based on season and geography.

**Results** The optimization model identifies the portfolio of interventions that minimizes net monetary cost and can solved more efficiently by exploiting linear separability and eliminating infeasible interventions before running the model. The optimal portfolio for WNV and Zika in the U.S. varied considerably by year.

**Conclusions** Our method enables systematic identification of the optimal blood safety portfolio in any setting. As our retrospective U.S. analysis demonstrates, the optimal portfolio can vary geographically, seasonally, and over time. We segmented donors by state, but another segmentation scheme could also be used. Employing this method with estimates of current or future TTI risk can inform more efficient blood safety policymaking.

**Keywords:** Blood safety, public health policy, binary integer programing, cost-effectiveness

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# Introduction

A safe supply of blood for transfusion is a critical component of the healthcare system in high-, middle-, and low-income countries alike (World Health Organisation, 2019). In most health systems, risk of transfusion-transmissible infections (TTIs) is managed through a portfolio of blood safety interventions. These portfolios consist of three types of interventions. *Donor deferral policies* turn away potential donors who have characteristics associated with increased risk for harboring a TTI. *Disease marker tests* are used to screen out donations with detectable disease markers. *Risk-reducing modifications* like pathogen inactivation or leukoreduction reduce the likelihood that a TTI, if present in a transfused donation, is transmitted to a recipient. Because of shifting epidemiological conditions, emerging infectious diseases, and new technologies, blood safety portfolios should be periodically reassessed. However, the number of available blood safety portfolios grows exponentially with the number of available interventions, making it impossible for policy makers to systematically enumerate, much less evaluate, all feasible portfolios without the assistance of a computer model.

In recent years, decision analytic modeling has played a growing role in informing decisions regarding blood safety portfolios. Because the health and economic consequences of a blood safety intervention depend on local epidemiological conditions, the existing blood safety portfolio, and the larger healthcare system, analyses of blood safety interventions are necessarily for a specific jurisdiction at a specific time. Most studies have been cost-utility analyses that incorporate relevant risks, costs, and health consequences. These studies typically consider adding or changing one intervention while keeping others constant. Several such analyses have been conducted to evaluate disease marker tests (Custer et al., 2005; El-Amine, Bish, & Bish, 2018; Jackson, Busch, Stramer, & AuBuchon, 2003; Russell, Stramer, Busch, & Custer, 2019), pathogen inactivation technologies (a new category of risk-reducing modifications) (Agapova et al., 2015; Bell et al., 2003; Custer, Agapova, & Martinez, 2010; Pereira, 1999), and donor deferral policies (Kort, Burg, Geerligs, Pieternel, & Marijt-van der Kreek, 2014). Methods have recently been proposed to systematically select a portfolio of disease marker tests for a specific context, assuming donor deferral and risk-reducing treatments interventions are held constant (Bish, Bish, Xie, & Stramer, 2014; Bish, Bish, Xie, & Slonim, 2011; Bish, El-Amine, Bish, Stramer, & Slonim, 2018). These optimization-based frameworks are designed to ensure that risk is sufficiently reduced, with considerations for waste and robustness, but are not designed to evaluate changes in deferral or modification interventions and are not necessarily consistent with finding the optimal policy from a cost-utility perspective.

In this paper, we develop a new framework for evaluating blood safety portfolios that uses a definition of optimality that is consistent with standard cost-utility analysis methods (Neumann, Ganiats, Russell, Sanders, & Siegel, 2016). In this framework, all relevant decision factors are expressed as costs or probabilities, and the set of blood safety decisions that minimizes the cost function is considered optimal. Unlike currently available methods, this framework enables the systematic comparison of all feasible portfolios of deferral, testing, and modification interventions to identify the portfolio that is preferred from a cost-utility perspective.

In the following sections, we derive our model by first introducing a simple model and progressively adding complexity. The model is a binary integer program (whether to implement each possible blood safety intervention). We discuss efficiency improvement techniques to reduce computation time in certain cases, and we apply the model to analyze U.S. policies for two TTIs that have been difficult to manage due to geographical and seasonal variations in prevalence and infectiousness, Zika virus and West Nile virus. We conclude with a discussion of implications and potential extensions of our modeling framework.

# Model Specification

In this section we derive our model by first developing the components for donor deferral, risk-reducing modification, and disease marker testing. All notation is summarized in Table 1.

## Donor deferral model

We begin with a simplified model for deciding whether to accept a donation based on risk of a single TTI. A donation may be infectious for the TTI () or not (), and the decision is to accept () or reject () the donation. If the donation is rejected (also called deferring the donor), a replacement cost is incurred because another donor must be recruited to meet demand. If the donation is accepted, a processing cost is incurred. We assume ; otherwise, the optimal decision would be to always reject donations regardless of blood safety concerns.

If the donation is accepted and is infectious for the TTI () then, in the absence of testing or modification interventions, an infectious donation is released for transfusion. Because donations are typically fractionated into multiple components, one infectious donation can expose multiple recipients to infection. We use the variable to represent the expected net monetary cost of releasing an infectious donation. We estimate this cost as , where is the net present expected cost of a breakthrough infectious donation, is the decision maker’s willingness to pay to avert the loss of one quality-adjusted life year (QALY), and is the net present expected QALYs lost. Estimating is a nontrivial exercise; its value depends on the TTI, the donor’s stage of infection, transfusion recipient characteristics, and how recipient exposures are treated.

Using the above notation, we express the cost function as follows:

For TTIs of concern, we assume (the net monetary cost of releasing an infectious donation exceeds the replacement cost of rejecting a donation), which ensures that optimal decision is to reject a donation if it is known to be infectious. In practice, a blood center does not know whether a donation will be infectious, but several methods are available for estimating the risk, which we denote with .

Given , the optimal policy is to choose (accept or reject) such that the expected cost is minimized:

From this equation, one can see that a decision maker should be indifferent between rejecting and accepting the donation when . When , the optimal decision is to accept the donation (), and when , the optimal decision is to reject the donation ().

Policymakers are typically concerned about multiple TTIs. We now consider multiple TTIs indexed by . We define a vector where entry indicates whether the potential donation is infectious for TTI , and a vector where entry () represents the expected cost of releasing a donation that is infectious for TTI . Our new cost function is

Taking the expectation, we obtain

where is a vector for which . The decision maker should reject the donation when , accept when , and be indifferent when .

Finally, we consider the case of deferral with multiple TTIs and donor groups. Rather than deciding whether to accept the entire donor population, policymakers often consider various donor groups, defined based on factors such as geographic location or the donor’s response to a pre-donation questionnaire. Donor groups may be defined in ways that facilitate temporary deferrals (e.g., “travel to Mexico within the past 60 days”) or according to the level of demand for the donor’s blood (e.g., by blood type).

We assume that the donor population has been segmented into mutually exclusive and exhaustive groups indexed by , and the decision to accept or reject donations from a specific group is represented by a vector with elements . We introduce a prevalence matrix with rows that correspond to donor groups and with columns that correspond to TTIs. Entry represents the risk of infectiousness for TTI in donations from donor group (i.e., ). We define where represents the replacement cost of a donation from group . It is possible that donor groups have different associated processing costs, so we define where represents the cost of processing a donation from group . Finally, we define where is the estimated number of donors from each group to present for donation in the period of analysis. Using this notation, the total expected cost of a given deferral policy is

where is a vector of all 1’s, in this case with length .

## Disease marker testing model

We now consider disease marker testing. We start with the case of one test for one TTI. We introduce a binary decision variable , where if the test is used and 0 otherwise. The test has an associated cost , sensitivity , and specificity . The probability of a positive test result is and the probability of a false negative is . We assume the blood center will always dispose of donations that test positive for a TTI, incurring a per donation cost of for a donation that tests positive. The constant should reflect the costs of any confirmatory testing, donor notification and counseling, and the cost of replacing the donation. Expected cost is

Note that not using a test is equivalent to using a test with sensitivity of 0 and specificity of 1; the expression will equal when and when t and the expression will equal when and will equal when . Using these, we can rewrite the cost function as

For the case of testing for more than one TTI, we define where is the sensitivity for detecting TTI , where is the specificity for detecting TTI , and is as defined above. The probability that a single test returns a negative result is . The probability that *any* TTI tests positive is one minus the probability that *all* TTIs test negative and is computed as . Using , the expected cost for one test and multiple TTIs is

We now consider multiple tests and multiple TTIs. We assume that tests are independent. We define a matrix where is the sensitivity of test for TTI and a matrix where is the specificity of test for TTI , and a vector where is the cost of test . We use the decision variable where when disease marker test is used.

Assuming that every available test is used, the probability of any positive result is . Replacing and with expressions that evaluate correctly when , we obtain .

To calculate the probability of a false negative test result for each TTI, we can take the element-wise product of and the following vector:

Using and , the expected cost function for multiple tests and multiple TTIs is

Finally, we develop an expected cost function for the case of multiple tests, TTIs, and donor groups. We define the decision variable where if test is used on donor group . To calculate the risk of each TTI in each group after tests are applied, we take the element-wise product of and the following matrix:

Additionally, we define a vector that represents the probability that a unit is disposed of in each donor group:

Using and , the expected cost function for multiple donor groups, TTIs, and tests is

## Risk-reducing modification model

Risk-reducing modifications (e.g., pathogen inactivation or leukoreduction) can decrease the risk of TTI in components derived from blood donations. We first consider one available modification and one TTI. We define as the risk-reduction multiplier for the modification and as the per-donation cost. Often, modifications are applied to only some of the components derived from a donation rather than the whole donation. For example, pathogen inactivation is currently FDA approved for platelet and plasma components but not red blood cells (Staley & Grossman, 2019). In this case, either can be scaled proportionally to the fraction of components modified or the same TTI in different components can be modeled as different TTIs (e.g. HIV in platelets vs. HIV in red blood cells). Because not applying a modification is equivalent to applying a modification with a risk multiplier of 1, we use the expression , which equals 1 when and when . Expected cost is

A modification can sometimes reduce the risk of multiple TTIs. We model this by introducing where is the risk-reduction multiplier for TTI . The expected cost for a single modification with multiple TTIs is

Often multiple modifications are available, each of which might reduce the risk for multiple TTIs. To model this, we define the vector where is the cost for modification , and where is the risk-reduction multiplier for modification and TTI . We replace the single decision variable with the vector where if modification is added to the portfolio. The product of risk-reducing multipliers for each modification in use can be calculated as follows:

Using this, the new expected cost is

Lastly, we integrate the model for multiple modifications with the model for multiple donor groups. We define a new decision variable where if modification is used on donor group . Because each element in must be multiplied by the product of any risk-reduction modifiers that are used in that sub-population, we define the following matrix:

Using this, the expected cost with multiple donor groups and modifications is as follows:

## Optimal portfolio model

Finally, we can write the expected cost function for a portfolio containing any combination of donor deferral policies, disease marker tests, and risk-reducing modifications:

This cost function expresses the net present net monetary cost of a policy (all future costs are discounted to present when calculating . The optimal combination of interventions is given by solving the following optimization problem:

The constraint ensures that no tests or modifications are applied to deferred donor groups.

The above formulation allows each non-deferred donor group to receive a tailored portfolio of tests and modifications. Health systems often use the same set of tests and modifications for all accepted donations regardless of donor group. Such policies may produce less benefit at a fixed willingness-to-pay than tailored policies but are easier to implement and might be perceived as fairer. To consider only universal testing and modification policies, two additional constraints can be introduced:

If tailored test and modify policies for each donor group are allowed, there will be feasible policies. If only universal test and modify policies are considered, the feasible state space will be which is smaller by a factor of approximately .

The cost function can be used to derive many other performance measures, summarized in Table 2, that may be more interpretable to policymakers. These performance measures can also be used to impose additional constraints on the optimization problem. For instance, one could limit the number of donors deferred (, where is an upper bound) or the total budget for tests and modifications (, where is an upper bound).

# Efficient Solutions

The optimal portfolio model is a binary integer program, and the exact solution can be found using exhaustive search. Because the state space increases exponentially in the number of available interventions, exhaustive search is not feasible for larger problems. Here we describe methods for more efficient identification of the optimal policy.

## Eliminate infeasible tests or modifications

Eliminating some tests or modifications from consideration in advance can considerably reduce the time needed to compute a solution for both the tailored and universal versions of the optimal portfolio problem. We can do so by leveraging the following theorem:

**Theorem 1:** *If use of a single test or modification is not preferred over using no interventions in any donor group it cannot be part of an optimal portfolio.*

To see why this theorem holds, consider the following. Tests and modifications reduce the cost function by reducing the multipliers on the expected cost of releasing an infectious donation (i.e., making the term smaller by decreasing one or more entries in and [tests] or [modifications]). Addition of a test or modification will generate the greatest reduction in expected cost when the term is largest, i.e. when no interventions are in use. Therefore, any test or modification that is part of an optimal portfolio will be preferred over a ‘no intervention’ scenario in at least one donor group.

## Tailored policies

When policies can be tailored to individual donor groups, the objective function is linearly separable, and we can solve a single, smaller optimization problem for each donor group. In this case we can identify the optimal portfolio by evaluating policies, rather than the evaluated by exhaustive search.

## Mapping the optimal policy to prevalence

In the case where donor groups are identical except with respect to the number of donors and the prevalence for each TTI , the optimal, a -dimensional function mapping the prevalence by TTI to the optimal policy can be defined as follows:

When the number of donor groups is large relative to the number of interventions, it can be more efficient to approximate this function than explicitly evaluate each donor group separately.

# Case study: West Nile and Zika Virus in the U.S.

Both West Nile virus (WNV) and Zika virus are most often transmitted by mosquitos but can also be transmitted by blood transfusion (Busch, Bloch, & Kleinman, 2019). For both diseases, more than 70% of infected individuals show no symptoms (Duffy et al., 2009; Petersen, Brault, & Nasci, 2013), creating a high risk of collecting a donation from an donor who is unaware of their infection. Additionally, incidence of both viruses varies geographically, seasonally, and annually, largely due to differences in mosquito population, necessitating regular reassessment of blood safety policy. Available interventions include nucleic acid testing (NAT), pathogen inactivation, and donor deferral. Currently, the United States mandates year-round mini-pooled (MP-)NAT testing for both Zika and WNV in all areas and requires that regions temporarily escalate to individual donation (ID-)NAT for WNV following the detection of confirmed positive (U.S. Food and Drug Administration, 2018; U.S. Food and Drug Association, 2009).

## Case study method

We applied our model to identify the optimal combinations of blood safety interventions for preventing transfusion-transmitted Zika and WNV in blood products derived from whole blood donations in the United States. We considered four screening tests, one risk-reducing modification, and 104 donor groups, segmented by geographic area and season. We identified the optimal portfolio separately for 2017, 2018, and 2019, and we compared metrics to two scenarios: universal MP-NAT for Zika and WNV and a ‘no intervention’ policy. Parameter values, shown in Table 3, were derived from the academic literature, Centers for Disease Control and Prevention (CDC) reports, and personal communications with blood safety experts. The optimization model was programmed in R. To estimate the harms of releasing a Zika- or WNV-infectious donation into the blood supply we developed microsimulation models of transfusion recipients in Python. All data and code will be uploaded to a public repository upon publication acceptance.

### Tests and modifications

We evaluated ID-NAT and MP-NAT for both WNV and Zika. In MP-NAT, the test is run on a pooled sample of 6-16 donations, with subsequent individual donation testing for any minipool that is initially reactive. MP-NAT can reduce the number of tests run per sample and therefore has a lower per-donation cost, but the test has a lower sensitivity. However, because the minipooled testing procedure requires both a reactive minipool and a subsequent reactive ID-NAT test, the risk of a false positive is greatly diminished. We considered four tests: Zika ID-NAT and MP-NAT as well as WNV ID-NAT and MP-NAT.

Pathogen inactivation (PI) is modification that can greatly reduce the transmission risk for many types of viruses and bacteria, including lipid-enveloped retroviruses like Zika and WNV (Prowse, 2013). However, PI is currently only approved for treating plasma or platelets components, not whole blood donations or red cell components, in the United States. Because platelet PI is typically done for apheresis rather than whole blood-derived platelets, We only included PI of whole blood-derived plasma as a possible blood safety intervention. We assumed that PI decreases risk of transmission by plasma exposure by 99% for both Zika and WNV. Based on our calculations using the 2015 National Blood Collection and Utilization Survey (Ellingson et al., 2017), plasma exposure accounts for 36% of the transfusion-transmission risk of an infectious donation, yielding a per-donation risk reduction multiplier around 65%.

### Donor groups

We included donors from 52 geographic areas (50 states, Puerto Rico, and the District of Columbia [DC]). We segmented donors based on geographic area and season. We estimated the total number of donations in a year from the 2015 National Blood Collection and Utilization Survey (NBCUS) (Ellingson et al., 2017) for the 50 states and D.C. and from Russell et al. (2019) for Puerto Rico. We assumed that the number of donors in each geographic area was proportional to the area’s population for a given year per U.S. Census Bureau estimates (United States Census Bureau, 2019). The probability of an infectious blood donation in the U.S. was based on CDC data on viremic blood donations interdicted by testing each year, and the risk assigned to an individual geographic area was assumed to be proportional to the number of CDC-reported symptomatic cases for that area (Centers for Disease Control and Prevention & Diseases, 2020a, 2020b). An analysis of CDC case reports by symptom onset date revealed that from 1999-2018, 99.1% of WNV cases occurred in the 6-month period from June to November (Centers for Disease Control and Prevention & Diseases, 2020a). We assumed that half the donations were collected during this ‘high mosquito season’ and the other donations were during ‘low mosquito season’ and assigned risk proportionally. Zika risk by season was proportional to that found in an earlier analysis of 2016-2017 data (Russell et al., 2019). Most Zika cases in the continental U.S. were travel-acquired, from either the northern or southern hemisphere, and did not exhibit the same seasonal trends as an outbreak driven by a local mosquito population. We therefore assumed that Zika risk in the continental United States did not change between the high and low mosquito seasons.

### Costs and QALYs

A 2014 analysis in the Netherlands estimated that the cost of a donation visit resulting in deferral cost the donor €16 in lost time and transportation and cost the blood center €2.65 – €31.82 depending on whether the donor was a routine donor or a first-time donor who needed to be recruited (Kort et al., 2014). The cost of recruiting, inviting, and evaluating a replacement donor cost €2.58 – €31.25, giving a total deferral cost of €21.23 for routine donors and €79.07 for first-time donors. Donors who are deferred are less likely to present to donate in the future than those who donate successfully (Custer et al., 2004), an additional cost not captured in the 2014 analysis. No data were available for the United States, so we assumed that the replacement cost for a deferred donor in the United States was $90. We also assumed a donation processing cost of $20 and a donation disposal cost of $60, which reflects confirmatory testing and donor notification costs.

To estimate the societal costs (medical expenses and productivity loss due to illness and death) and QALYs lost that result from transfusion-transmission, we developed separate microsimulations for each disease (Zika and WNV). We adapted the model structure from a prior publication (Russell et al., 2019). Both models simulated individual transfusion recipients whose age, sex, and number of red blood cell, platelet and plasma components transfused followed a similar distribution to transfusion recipients in the United States. The expected post-transfusion survival for each recipient was calculated as a function of age and the number and type of blood components transfused (Russell et al., 2019). For the Zika model, we adapted parameters including probabilities, costs, and QALY multipliers for Zika fever and more severe sequelae from the prior publication and updated to 2019 US dollars using the personal healthcare component of the National Health Expenditure Data provided by the Centers for Medicare and Medicaid Services (Centers for Medicare and Medicaid Services, 2019). The Zika model also captured costs and QALY losses due to secondary sexual or congenital transmission of Zika to a transfusion recipient’s sexual partner or offspring (Figure 1A). In the WNV model, recipients could experience asymptomatic infection, acute WNV fever, or one of three neurological diseases (meningitis, encephalitis, or acute flaccid paralysis). Secondary transmission was not modeled (Figure 1B). Transfusion recipients experiencing acute disease were also at risk for long-term disability. The WNV model was developed using parameter values from a recent cost-effectiveness analysis of a WNV vaccine (Shankar, Staples, Meltzer, & Fischer, 2017) as well as a study of the costs of WNV infection (Staples, Shankar, Sejvar, Meltzer, & Fischer, 2014) with costs updated to 2019 US dollars. In both microsimulations, costs and QALYs lost were discounted to net present using an annual discount rate of 3%. The decision tree structures for the two models are shown in Supplemental Figure S1, and all model parameters are listed in Supplemental Tables S1 and S2.

The recipient microsimulations estimate the outcomes in recipients who receive different number and types of whole blood-derived components. We estimated the average outcome by component type with the following weighted average approach:

where outcome is cost or QALYs lost due to disease , is the blood component type, indexes individual transfusion recipients, and is the number units of component transfused to recipient . To estimate the expected net health costs of releasing an infectious donation, the average number components transfused per whole blood donation collected was estimated from the 2015 NBCUS (Ellingson et al., 2017) and the component-specific probability of transfusion-transmission for both WNV and Zika were estimated from literature (Custer, Johnson, et al., 2005; Russell et al., 2019). The expected value of the outcomes (cost and QALY loss) per donation were then calculated as follows:

where is the probability of that disease is transmitted to a recipient exposed to an enfectious component of type , and is the average number of units of component tye produced per whole blood donation. This procedure was used to estimate both cost and QALYs lost, which were then used to calculate net health cost was calculated assuming a willingness-to-pay threshold of $1 million per QALY in the base case (Custer & Hoch, 2009).

### Uncertainty analysis

We performed probabilistic sensitivity analysis by repeating the analysis 10,000 times using input parameters randomly sampled from the probability distributions listed in Table 3 and Supplemental Tables S1 and S2. We calculated performance metrics and tracked how often each intervention was part of the optimal portfolio across all 10,000 iterations. Prevalence and willingness-to-pay were not varied in probabilistic sensitivity analysis but were analyzed in scenario analysis. For this analysis we first estimated the optimal policy for a single donor group as a function WNV and Zika prevalence by computing the optimal policy for 10,000 pairs of WNV and Zika prevalence values. To assess the impact of varying willingness-to-pay, we repeated this analysis for values of $100,000 and $10,000,000 per QALY, in addition to the base case value of $1,000,000 per QALY.

## Results of case study

On average, releasing a Zika-infectious donation would result in an estimated loss of 0.0082 QALYs (95% CrI, 0.0011 – 0.028 QALYs) and $1,574 in societal costs (95% CrI, $347 – $4,676). On average, releasing a WNV-infectious donation would result in an estimated loss of 0.031 QALYs (95% CrI, 0.024 – 0.046 QALYs) and $6,595 in societal costs (95% CrI, $1,241 – $10,239). Using a willingness-to-pay of $1 million per QALY gained, the estimated expected net monetary cost of releasing infectious donations for transfusion was $9,739 (95% CrI, $1,452 – $32,312) for Zika and $37,992 (95% CrI, $26,495 – $52,499) for WNV. In a given calendar year there were 8.42e+157 possible portfolios tailored by state. By leveraging linear separability, the optimal portfolio could be identified by evaluating 3328 policies.

In the basecase, the only intervention that was part of the optimal portfolio was WNV MP-NAT, which was optimal during the high mosquito season in five states in 2017 (ND, SD, NE, NV, and MS) and in 5 states in 2018 (ND, SD, NE, MT, and IA). In 2019 it was optimal to use no intervention. In PSA, Zika testing was sometimes optimal in Puerto Rico in 2017 (with MP-NAT 19.6% of iterations and ID-NAT 0.94%). For many states, WNV MP- or ID-NAT was optimal in some PSA iterations, showin in Figure 2. There was considerable variation by year, and in no state was WNV testing optimal in most iterations across all 3 years. Supplemental Table S4 provides full details on how frequently interventions were optimal in PSA iterations by area.

By most performance measures, the optimal portfolio was closer to a policy of no intervention than a policy of universal MP-NAT (Table 4). **[I’m planning to replace these results with a ZIP code level analysis, so not fully discussing them for now. At the state level, the optimal policy doesn’t prevent much TTI infection, but hopefully it wil lbe much better at Zip code level. I’m thinking I will move the state-level stuff to the supplement and contrast it with the ZIP code results to emphasize how donor segmentation scheme can influence how well the optimal portfolio performs.]**

For donor groups with Zika and WNV prevalence between 1e-6 to 0.3 per donation, one of 13 policies may be optimal as shown in Figure 3. These range from no intervention for low Zika and WNV prevalence levels to deferal for high prevalence levels, with various testing combinations indicated for intermediate prevalence levels. As Figure 3 shows, increasing the willingness-to-pay threshold makes it optimal to apply interventions at lower prevalence levels. Figure S1 visualizes five performance measures for the optimal policy as a function of Zika and WNV prevalence. Because each intervention is binary, measures like the optimal policy’s residual risk, testing cost, and downstream net monetary cost are not smooth functions of prevalence. Because the objective function value is minimizing a function composed of these performance measures, it is a smoother function of TTI prevalence.

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# Discussion

Selecting a portfolio of blood safety interventions is a tremendous challenge for blood collection agencies and regulatory bodies worldwide. Epidemiologic variation leads to changes in TTI risk across populations and over time, and the characteristics of available interventions change as economic conditions shift and new technologies become available. These factors necessitate that blood safety portfolios are optimized for local conditions and are reassessed periodically. Our framework is the first method capable of selecting the optimal portfolio from a set of deferral, testing, or modification interventions for any TTIs.

In our case study, we applied this framework to evaluate interventions for WNV and Zika in 2017, 2018, and 2019. Our analysis was limited to whole blood donations, and a similar analysis might identify a different optimal portfolio for apheresis platelet, plasma, or red blood cell donations. Use of plasma pathogen inactivation was never optimal in our analysis, but our analysis considered only two of the many viruses and bacteria inactivated and therefore did not capture the full benefit of PI. Importantly, our case study was a retrospective analysis of what would have been optimal given perfect information about prevalence. To best inform policymaking, our framework would need to be combined with projections of current and future risks, not past risks.

Our framework is designed to identify the optimal portfolio of all interventions for all TTIs of concern in a given jurisdiction. However, a comprehensive analysis will require significant effort. While most blood safety cost-effectiveness analysis evaluate the downstream societal costs and QALY losses for a single TTI, evaluating all interventions will require a similar analysis of all TTIs for which risk is impacted. Additionally, donor segmentation is challenging when TTIs with different types of risk factors are considered in the same analysis. For example, geography and season are natural dimensions for segmenting donors based on WNV and Zika risk, but behavioral risk factors are far more relevant for HIV and hepititis C, two major TTIs. Optimal definition of donor groups, particularly with TTIs with different types of risk factors, is an important area for further research.

By identifying the portfolio that minimizes net present net monetary costs, our framework is consistent with cost-effectiveness, the most common analysis used to evaluate blood safety interventions. However, policymakers may have addition considerations, such as fixed intervention budgets or a preconceived notion of the acceptable level of risk. Such considerations could be incorporated into the model through additional constraints or modifications of the cost function. Additionally, many modeling assumptions in our framework are simplifications of reality. For instance, the framework assumes independence across tests and modifications, while in reality tests for the same TTI may be highly correlated, particularly when they are either both nucleic acid tests (designed to detect the virus’ DNA or RNA directly) or both serological tests (designed to detect the donor’s antibody response). Additionally, our framework assumes the cost of replacing a donation does not depend on how many donations need to be replaced. However, the donation replacement cost may increase at higher deferral rates due to the difficulty of recruiting new donors once the regular donor pool is exhausted. Our framework could be modified to adress such limitations, but at the potential cost of increased computational complexity. While our framework is designed to maximize expected utility, it could be combined with methods such as robust and stochastic optimization to incorporate different utility functions and objectives.

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Table 1. Summary of notation

* : single variable
* with elements : vector
* with elements : matrix
* : indicator variable
* : vector for which every entry is 1
* : probability equals
* : Hadamard (element-wise) product of same-dimensioned vectors or matrices

###### Indices

* : transfusion-transmissible infections (TTIs)
* : segments of the donor population
* : available disease marker tests
* : available risk-reducing modifications

###### Decision variables

* where : 1 if donations from donor group are accepted
* where : 1 if modification is used in donations from donors in group
* where : 1 if disease marker test is used for donations from donors in group

###### Parameters related to transfusion-transmissible infections (TTIs)

* where : 1 if a donor is infectious with TTI
* where : probability that a donor is infectious with TTI
* where : net health cost of releasing a donation infectious for TTI

###### Parameters related to donor groups

* where : probability a donation from donor group will be infectious for TTI
* where : cost of replacing a deferred donation from a deferred donor from group
* where : cost of processing a donation for a donor from group
* where : number of donors in subgroup

###### Parameters related to disease marker tests

* where : per-donation cost of disease marker test
* where : sensitivity of test for TTI
* where : specificity of test for TTI
* : disposal cost for collected donations that test positive

###### Parameters related to modification interventions

* where : per-donation cost of modification intervention
* where : percent reduction in risk of TTI from modification intervention

##### 

Table 2. Key policy measures

|  |  |
| --- | --- |
| **Measure** | **Formula** |
| Risk reduction for TTI in group by testing () |  |
| Risk reduction for TTI in group by modifications () |  |
| Residual risk for TTI in group (returns ) |  |
| Donation yield |  |
| Residual risk of infection for TTI () |  |
| Number of infectious donations released for TTI () |  |
| Total modification cost |  |
| Total cost of initial tests |  |
| Total donor replacement cost |  |
| Total processing cost |  |
| Total cost due to released infectious donations |  |
| Total cost due to removed donations testing positive |  |
| Number of donations testing positive |  |

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Table 3. Parameters for optimization model

Abbreviations: FFP, fresh and frozen plasma, ID-, individual donation, MP-, minipooled, NAT, nucleic acid testing, PI, pathogen inactivation, Tri, triangular distribution, WNV, West Nile virus.

| **Parameter** | **Value (range)** | **Distribution** |
| --- | --- | --- |
| Donation replacement cost | $90 (45—135) | Tri |
| Donation processing cost | $20 (10—30) | Tri |
| Donation disposal cost (excluding replacement) | $60 (30—90) | Tri |
| Zika ID-NAT cost per donation | $10 (5—15) | Tri |
| Zika MP-NAT cost per donation | $6 (3—9) | Tri |
| WNV ID-NAT cost per donation | $10 (5—15) | Tri |
| WNV MP-NAT cost per donation | $6 (3—9) | Tri |
| Sensitivity of Zika ID-NAT for Zika | 0.999 (0.998—1) | Tri |
| Sensitivity of Zika MP-NAT for Zika | 0.98 (0.961—0.999) | Tri |
| Sensitivity of WNV ID-NAT for WNV | 0.99 (0.98—1) | Tri |
| Sensitivity of WNV MP-NAT for WNV | 0.95 (0.91—0.99) | Tri |
| Specificity of Zika ID-NAT for Zika | 0.9997 (0.9994—1) | Tri |
| Specificity of Zika MP-NAT for Zika | 0.999999999 (0.999999998—1) | Tri |
| Specificity of WNV ID-NAT for WNV | 0.9997 (0.9994—1) | Tri |
| Specificity of WNV MP-NAT for WNV | 0.999999999 (0.999999998—1) | Tri |
| Cost of FFP PI | $81 (40.64—121.92) | Tri |
| Risk reducing multiplier of FFP PI for Zika | 0.645664139 (0.5165313112—0.7747969668) | Tri |
| Risk reducing multiplier of FFP PI for WNV | 0.64287943 (0.514303544—0.771455316) | Tri |
| Red blood cell units transfused per donation | 0.944 (0.908—0.98) | Tri |
| Platelet units transfused per donation | 0.015 (0.012—0.018) | Tri |
| Plasma units transfused per donation | 0.541 (0.4328—0.6492) | Tri |
| Transmissibility of Zika in RBC components | 0.5 (0.3—0.7) | Tri |
| Transmissibility of Zika in PLT components | 0.5 (0.3—0.7) | Tri |
| Transmissibility of Zika in FFP components | 0.9 (0.8—1) | Tri |

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Table 4. Performance of optimal policy compared to universal testing and not testing

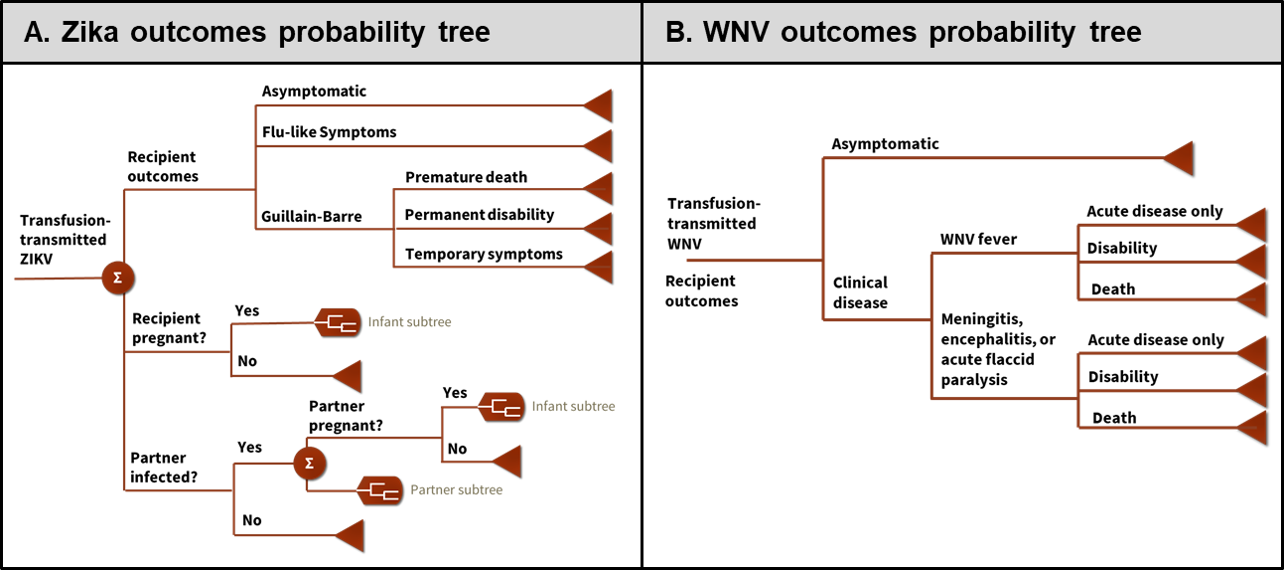
Basecase values reported with 95% credible interval from probabilistic sensitivity analysis. Abbreviations: MP-NAT, minipooled nucleic acid testing.

| **year** | **Optimal** | **No intervention** | **Universal MP-NAT** |
| --- | --- | --- | --- |
| **Objective function value** | | | |
| 2017 | $216.35M ($136.06M—$296.44M) | $216.96M ($136.73M—$297.17M) | $331.02M ($242.93M—$418.85M) |
| 2018 | $218.00M ($137.20M—$297.76M) | $220.70M ($140.25M—$301.26M) | $331.23M ($243.08M—$418.96M) |
| 2019 | $210.35M ($130.03M—$290.61M) | $210.35M ($130.32M—$290.62M) | $330.67M ($242.66M—$418.45M) |
| **Test cost** | | | |
| 2017 | $0.90M ($0.30M—$4.93M) | $0.00M ($0.00M—$0.00M) | $123.92M ($89.54M—$158.58M) |
| 2018 | $0.73M ($0.61M—$3.45M) | $0.00M ($0.00M—$0.00M) | $123.92M ($89.54M—$158.58M) |
| 2019 | $0.00M ($0.00M—$1.40M) | $0.00M ($0.00M—$0.00M) | $123.92M ($89.54M—$158.58M) |
| **Net monitary cost of released infectious donations** | | | |
| 2017 | $8.91M ($5.29M—$11.36M) | $10.42M ($7.31M—$14.37M) | $0.51M ($0.18M—$0.92M) |
| 2018 | $10.26M ($6.93M—$12.33M) | $14.16M ($9.88M—$19.56M) | $0.71M ($0.25M—$1.28M) |
| 2019 | $3.81M ($2.23M—$4.39M) | $3.81M ($2.66M—$5.26M) | $0.19M ($0.07M—$0.35M) |
| **Zika residual risk** | | | |
| 2017 | 3.10e-06 (1.48e-06—3.10e-06) | 3.10e-06 (3.10e-06—3.10e-06) | 6.20e-08 (1.68e-08—1.08e-07) |
| 2018 | 2.90e-07 (2.91e-07—2.91e-07) | 2.90e-07 (2.91e-07—2.91e-07) | 5.81e-09 (1.57e-09—1.01e-08) |
| 2019 | 4.84e-08 (4.84e-08—4.84e-08) | 4.84e-08 (4.84e-08—4.84e-08) | 9.68e-10 (2.62e-10—1.69e-09) |
| **WNV residual risk** | | | |
| 2017 | 2.19e-05 (1.13e-05—2.35e-05) | 2.58e-05 (2.58e-05—2.58e-05) | 1.29e-06 (4.82e-07—2.08e-06) |
| 2018 | 2.60e-05 (1.91e-05—2.63e-05) | 3.60e-05 (3.60e-05—3.60e-05) | 1.80e-06 (6.74e-07—2.91e-06) |
| 2019 | 9.69e-06 (5.64e-06—9.69e-06) | 9.69e-06 (9.69e-06—9.69e-06) | 4.85e-07 (1.82e-07—7.83e-07) |
| **Zika-infectious donations released** | | | |
| 2017 | 32.00 (15.30—32.00) | 32.00 (32.00—32.00) | 0.64 (0.17—1.11) |
| 2018 | 2.99 (3.00—3.00) | 3.00 (3.00—3.00) | 0.06 (0.02—0.10) |
| 2019 | 0.50 (0.50—0.50) | 0.50 (0.50—0.50) | 0.01 (0.00—0.02) |
| **WNV-infectious donations released** | | | |
| 2017 | 226.22 (116.75—242.58) | 266.00 (266.06—266.06) | 13.30 (4.98—21.49) |
| 2018 | 268.84 (197.00—271.43) | 372.00 (371.96—371.96) | 18.59 (6.96—30.04) |
| 2019 | 100.09 (58.29—100.09) | 100.09 (100.09—100.09) | 5.00 (1.87—8.09) |

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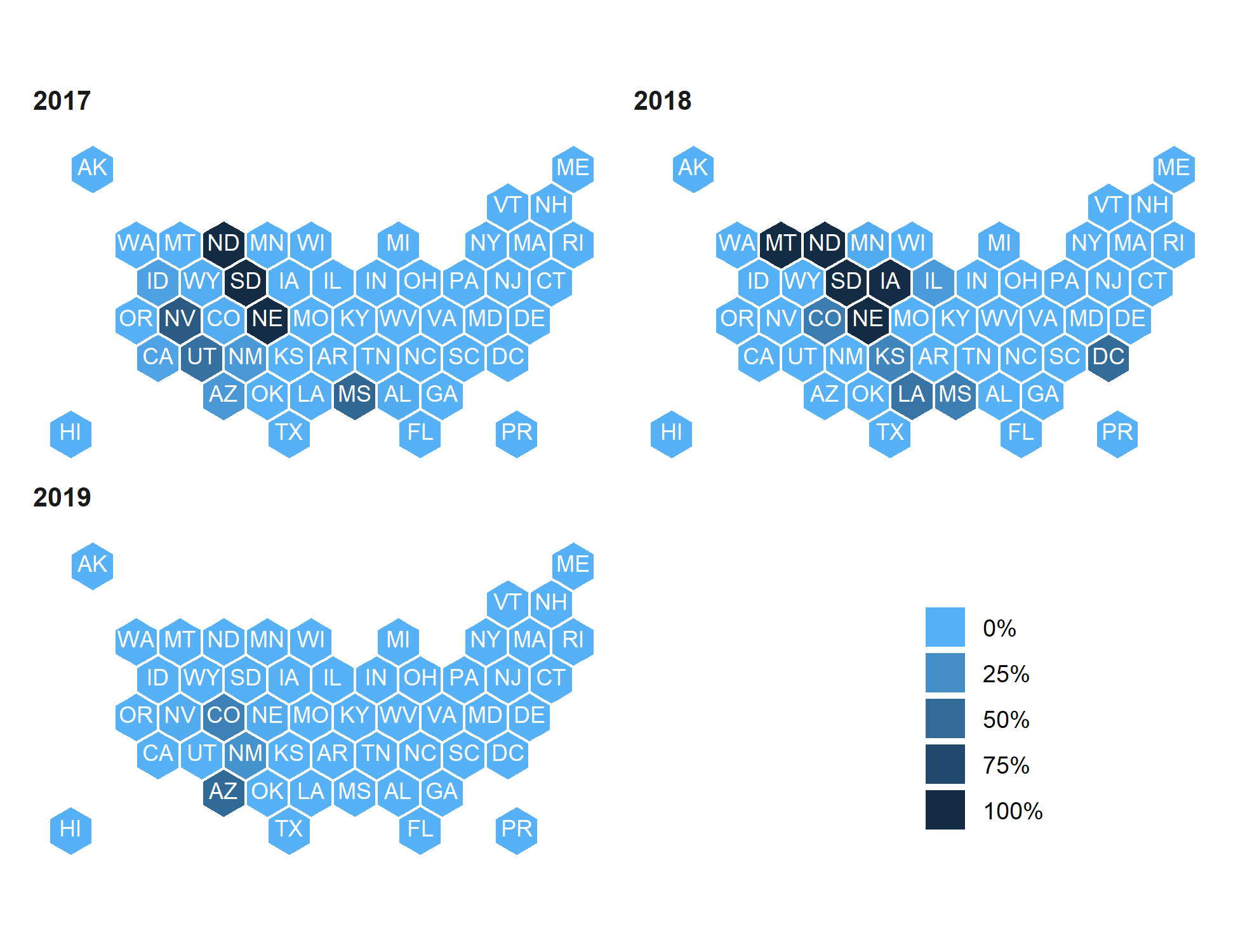
Figure 1.Probability trees simulated in the recipient outcomes microsimulation for Zika (A) and for West Nile virus (B).

Infant and partner subtrees for Zika microsimulation are reported in Russell et al. (2019). Abbreviations: WNV, West Nile virus; ZIKV, Zika virus



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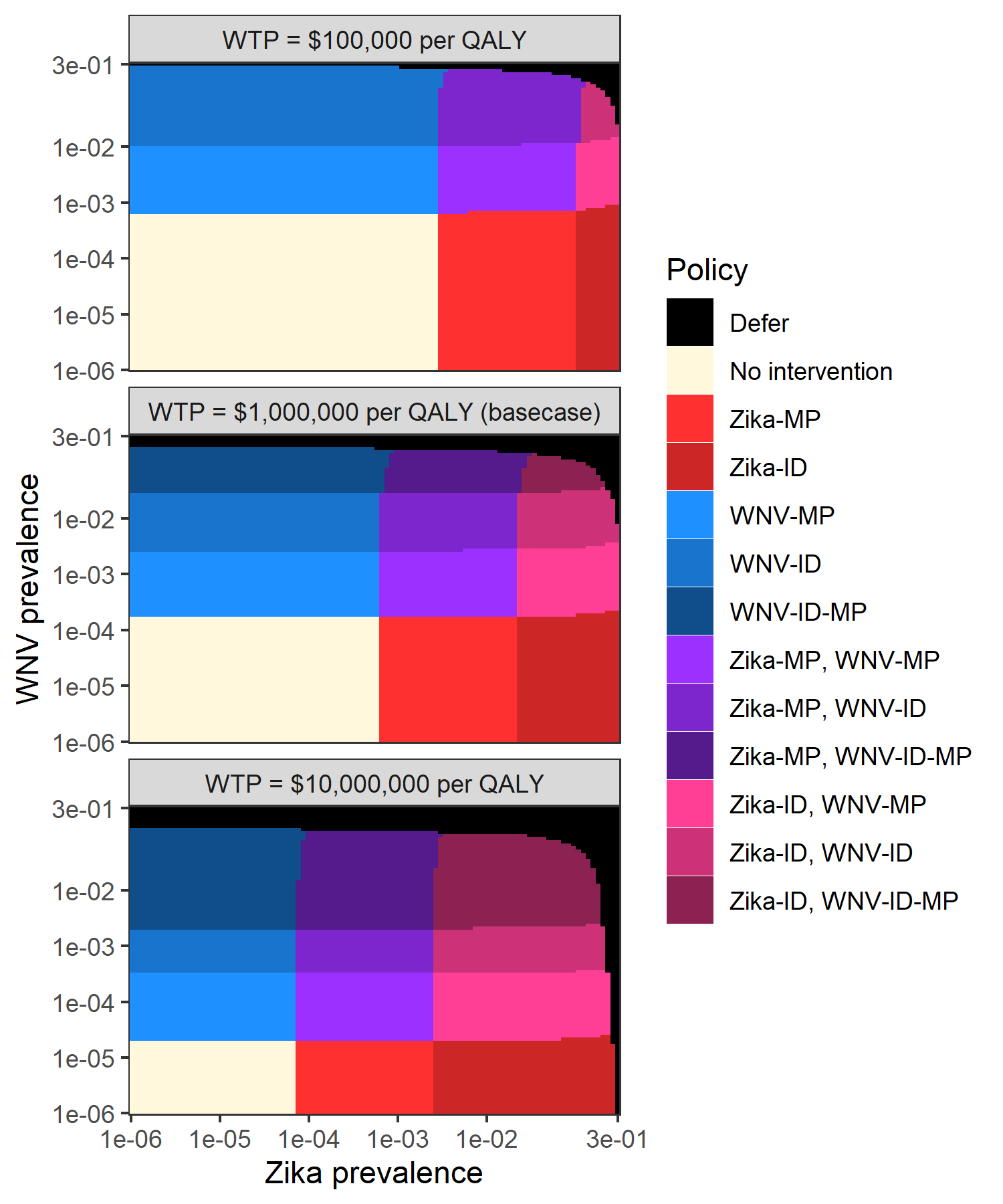
Figure 2.Hexbin map showing percent of probabilistic sensitivity analysis iterations for which WNV testing during high mosquito season was optimal by geographic area in 2017, 2018, and 2019



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Figure 3. Optimal policy as a function of WNV and Zika prevalence for various willingness-to-pay levels

The optimal policy for an individual donor group was identified for all 10,000 combinations of 100 Zika and 100 WNV prevalence values, evenly spaced on a logarithmic scale from 1e-6 to 0.3. Abbreviations: WNV, West Nile virus. In the three scenarios, net monetary cost of releasing a Zika- or WNV-infectious donation was re-calculated with a different willingness to pay per QALY gained. Abbreviations: -ID, individual donation nucleic acid testing, -MP, minipooled nucleic acid testing, QALY, quality-adjusted life year; WNV, West Nile virus.



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Optimal portfolios of blood safety interventions: test, defer or modify?

Supplement

#### W. Alton Russell, Brian Custer, Margaret L. Brandeau

## Estimating the potential value of a novel test or modification

It is possible to develop insight into the potential utility of a new test or modification for blood banking before the technology has been developed. By making pessimistic assumptions about the risk of disease in the donor populations and optimistic simplifications about the efficacy and costs of an interventions, we have developed simple criteria that can remove infeasible interventions from consideration. For a given test (with index ) or a given modification (with index ) that influences risk for only one disease (with index ), the following must hold for the intervention to be part of an optimal portfolio:

The quantity is the value of the intervention assuming it eliminates all risk of infection for disease in the donor group with the highest risk, without incurring any additional costs (e.g., replacing donations testing positive). If the per-donation cost of a test () or modification () are not below that quantity, the intervention can be removed from consideration.

For interventions that reduce the risk for multiple disease we can use a generalization requiring for the inequality to hold for all donor groups (unless the analyst identifies one donor group which has the highest risk for all diseases influenced by the intervention). The conditions for interventions influencing risk for multiple disease are:

Where indicates the diseases a given test can detect and indicates the disease for which the modification reduces risk.

While these conditions were derived for eliminating interventions from consideration with the optimal portfolio model, they can be applied more generally to eliminate tests and modifications from consideration.

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Table S1. Number of donors and prevalence of Zika and WNV by donor group

Donor groups defined by state-level geographic area (also includes Washington D.C. and Puerto Rico), year, and season. Prevalence estimated by weighting the nucleic acid test-reactive donations by the case reports from the Centers for Disease Control and Prevention. Abbreviations: WNV, West Nile virus

|  | **Year** | **Donors, N** | **WNV prevalence** | | **Zika prevalence** | |
| --- | --- | --- | --- | --- | --- | --- |
| **Geographic area** | **High season** | **Low season** | **High season** | **Low season** |
| Alabama (AL) | 2017 | 153726 | 9.8e-05 | 8.5e-07 | 5.8e-07 | 5.8e-07 |
| 2018 | 153338 | 5.1e-05 | 4.4e-07 | 1.8e-07 | 1.8e-07 |
| 2019 | 153098 | 7.1e-06 | 6.1e-08 | 0 | 0 |
| Alaska (AK) | 2017 | 23328 | 0 | 0 | 2.6e-06 | 2.6e-06 |
| 2018 | 23064 | 1.2e-05 | 1e-07 | 0 | 0 |
| 2019 | 22842 | 9.5e-06 | 8.2e-08 | 0 | 0 |
| Arizona (AZ) | 2017 | 222146 | 0.00013 | 1.1e-06 | 4e-07 | 4e-07 |
| 2018 | 224566 | 3.2e-05 | 2.8e-07 | 1.2e-07 | 1.2e-07 |
| 2019 | 227272 | 0.00017 | 1.4e-06 | 0 | 0 |
| Arkansas (AR) | 2017 | 94652 | 4.8e-05 | 4.1e-07 | 0 | 0 |
| 2018 | 94422 | 2.4e-05 | 2e-07 | 0 | 0 |
| 2019 | 94228 | 2.1e-05 | 1.8e-07 | 0 | 0 |
| California (CA) | 2017 | 1241240 | 0.00011 | 9.7e-07 | 1.2e-06 | 1.2e-06 |
| 2018 | 1238008 | 4.9e-05 | 4.2e-07 | 2.8e-07 | 2.8e-07 |
| 2019 | 1233736 | 3.7e-05 | 3.2e-07 | 2e-08 | 2e-08 |
| Colorado (CO) | 2017 | 176980 | 9.7e-05 | 8.4e-07 | 1e-06 | 1e-06 |
| 2018 | 178550 | 0.00015 | 1.3e-06 | 0 | 0 |
| 2019 | 179812 | 0.00015 | 1.3e-06 | 0 | 0 |
| Connecticut (CT) | 2017 | 112690 | 6.7e-06 | 5.8e-08 | 2.1e-06 | 2.1e-06 |
| 2018 | 112048 | 5.7e-05 | 5e-07 | 0 | 0 |
| 2019 | 111324 | 1.9e-06 | 1.7e-08 | 0 | 0 |
| Delaware (DE) | 2017 | 30176 | 8.3e-06 | 7.2e-08 | 0 | 0 |
| 2018 | 30290 | 9.2e-05 | 8e-07 | 0 | 0 |
| 2019 | 30404 | 0 | 0 | 0 | 0 |
| District of Columbia (DC) | 2017 | 21916 | 4.6e-05 | 4e-07 | 4.1e-06 | 4.1e-06 |
| 2018 | 22010 | 0.00016 | 1.4e-06 | 0 | 0 |
| 2019 | 22036 | 6.9e-05 | 6e-07 | 0 | 0 |
| Florida (FL) | 2017 | 661126 | 1.9e-06 | 1.6e-08 | 5e-06 | 5e-06 |
| 2018 | 666488 | 1.5e-05 | 1.3e-07 | 2.9e-07 | 2.9e-07 |
| 2019 | 670624 | 6.4e-07 | 5.6e-09 | 0 | 0 |
| Georgia (GA) | 2017 | 328308 | 3.7e-05 | 3.2e-07 | 1.8e-07 | 1.8e-07 |
| 2018 | 329760 | 3e-05 | 2.6e-07 | 0 | 0 |
| 2019 | 331520 | 9.1e-06 | 7.9e-08 | 3.8e-08 | 3.8e-08 |
| Hawaii (HI) | 2017 | 44920 | 0 | 0 | 4e-06 | 4e-06 |
| 2018 | 44568 | 0 | 0 | 0 | 0 |
| 2019 | 44210 | 0 | 0 | 0 | 0 |
| Idaho (ID) | 2017 | 54172 | 0.00012 | 1e-06 | 0 | 0 |
| 2018 | 54918 | 8.1e-05 | 7e-07 | 0 | 0 |
| 2019 | 55800 | 4.3e-05 | 3.7e-07 | 1.1e-07 | 1.1e-07 |
| Illinois (IL) | 2017 | 403004 | 5.6e-05 | 4.9e-07 | 5.2e-07 | 5.2e-07 |
| 2018 | 399154 | 0.00012 | 1.1e-06 | 1e-07 | 1e-07 |
| 2019 | 395666 | 1.3e-05 | 1.1e-07 | 0 | 0 |
| Indiana (IN) | 2017 | 209974 | 3.1e-05 | 2.7e-07 | 4.3e-07 | 4.3e-07 |
| 2018 | 210054 | 4.6e-05 | 4e-07 | 0 | 0 |
| 2019 | 210208 | 4.1e-06 | 3.6e-08 | 0 | 0 |
| Iowa (IA) | 2017 | 99074 | 3e-05 | 2.6e-07 | 3e-07 | 3e-07 |
| 2018 | 98780 | 0.00029 | 2.5e-06 | 0 | 0 |
| 2019 | 98514 | 1.1e-05 | 9.5e-08 | 0 | 0 |
| Kansas (KS) | 2017 | 91732 | 7.4e-05 | 6.4e-07 | 6.5e-07 | 6.5e-07 |
| 2018 | 91336 | 0.00014 | 1.2e-06 | 0 | 0 |
| 2019 | 90966 | 1.4e-05 | 1.2e-07 | 0 | 0 |
| Kentucky (KY) | 2017 | 140410 | 1.8e-05 | 1.6e-07 | 4.3e-07 | 4.3e-07 |
| 2018 | 139958 | 2.4e-05 | 2.1e-07 | 0 | 0 |
| 2019 | 139500 | 1.5e-06 | 1.3e-08 | 0 | 0 |
| Louisiana (LA) | 2017 | 147294 | 9.1e-05 | 7.8e-07 | 2e-07 | 2e-07 |
| 2018 | 146186 | 0.00016 | 1.4e-06 | 0 | 0 |
| 2019 | 145154 | 3e-05 | 2.6e-07 | 0 | 0 |
| Maine (ME) | 2017 | 42090 | 0 | 0 | 7.1e-07 | 7.1e-07 |
| 2018 | 42010 | 1.3e-05 | 1.2e-07 | 0 | 0 |
| 2019 | 41972 | 0 | 0 | 0 | 0 |
| Maryland (MD) | 2017 | 189974 | 7.9e-06 | 6.9e-08 | 1.7e-06 | 1.7e-06 |
| 2018 | 189358 | 6.6e-05 | 5.7e-07 | 1.4e-07 | 1.4e-07 |
| 2019 | 188772 | 3.4e-06 | 3e-08 | 0 | 0 |
| Massachusetts (MA) | 2017 | 216336 | 7e-06 | 6e-08 | 1.7e-06 | 1.7e-06 |
| 2018 | 215926 | 6.3e-05 | 5.5e-07 | 6.3e-08 | 6.3e-08 |
| 2019 | 215212 | 5e-06 | 4.4e-08 | 0 | 0 |
| Michigan (MI) | 2017 | 314520 | 3.2e-05 | 2.8e-07 | 6.6e-07 | 6.6e-07 |
| 2018 | 313226 | 9.1e-05 | 7.9e-07 | 0 | 0 |
| 2019 | 311832 | 8.3e-06 | 7.2e-08 | 0 | 0 |
| Minnesota (MN) | 2017 | 175542 | 4.3e-05 | 3.7e-07 | 1.4e-06 | 1.4e-06 |
| 2018 | 175882 | 1e-04 | 8.7e-07 | 7.8e-08 | 7.8e-08 |
| 2019 | 176092 | 3.7e-06 | 3.2e-08 | 0 | 0 |
| Mississippi (MS) | 2017 | 94248 | 0.00017 | 1.5e-06 | 6.3e-07 | 6.3e-07 |
| 2018 | 93522 | 0.00015 | 1.3e-06 | 0 | 0 |
| 2019 | 92928 | 3.5e-05 | 3e-07 | 0 | 0 |
| Missouri (MO) | 2017 | 192584 | 2.5e-05 | 2.2e-07 | 3.1e-07 | 3.1e-07 |
| 2018 | 192050 | 3.3e-05 | 2.9e-07 | 0 | 0 |
| 2019 | 191636 | 3.4e-06 | 2.9e-08 | 0 | 0 |
| Montana (MT) | 2017 | 33192 | 8.3e-05 | 7.2e-07 | 0 | 0 |
| 2018 | 33276 | 0.00039 | 3.4e-06 | 0 | 0 |
| 2019 | 33372 | 1.9e-05 | 1.7e-07 | 0 | 0 |
| Nebraska (NE) | 2017 | 60422 | 0.00028 | 2.5e-06 | 9.9e-07 | 9.9e-07 |
| 2018 | 60412 | 0.0012 | 1e-05 | 0 | 0 |
| 2019 | 60400 | 0.0001 | 8.7e-07 | 1e-07 | 1e-07 |
| Nevada (NV) | 2017 | 93662 | 0.00018 | 1.6e-06 | 3.2e-07 | 3.2e-07 |
| 2018 | 94976 | 2.6e-05 | 2.3e-07 | 0 | 0 |
| 2019 | 96176 | 9.9e-05 | 8.6e-07 | 6.5e-08 | 6.5e-08 |
| New Hampshire (NH) | 2017 | 42536 | 5.9e-06 | 5.1e-08 | 0 | 0 |
| 2018 | 42462 | 0 | 0 | 0 | 0 |
| 2019 | 42456 | 0 | 0 | 0 | 0 |
| New Jersey (NJ) | 2017 | 280220 | 7.2e-06 | 6.2e-08 | 1.3e-06 | 1.3e-06 |
| 2018 | 278776 | 6.1e-05 | 5.3e-07 | 2.4e-07 | 2.4e-07 |
| 2019 | 277338 | 6.2e-06 | 5.4e-08 | 6.8e-08 | 6.8e-08 |
| New Mexico (NM) | 2017 | 65968 | 0.00013 | 1.1e-06 | 0 | 0 |
| 2018 | 65654 | 3e-05 | 2.6e-07 | 0 | 0 |
| 2019 | 65472 | 0.00013 | 1.2e-06 | 0 | 0 |
| New York (NY) | 2017 | 617792 | 2.1e-05 | 1.8e-07 | 3.1e-06 | 3.1e-06 |
| 2018 | 612716 | 4.5e-05 | 3.9e-07 | 1.8e-07 | 1.8e-07 |
| 2019 | 607420 | 5.7e-06 | 4.9e-08 | 3.1e-08 | 3.1e-08 |
| North Carolina (NC) | 2017 | 323828 | 6.2e-06 | 5.4e-08 | 7.4e-07 | 7.4e-07 |
| 2018 | 325698 | 8.6e-06 | 7.4e-08 | 1.3e-07 | 1.3e-07 |
| 2019 | 327482 | 6.6e-07 | 5.7e-09 | 0 | 0 |
| North Dakota (ND) | 2017 | 23808 | 0.00065 | 5.7e-06 | 0 | 0 |
| 2018 | 23782 | 0.0024 | 2.1e-05 | 0 | 0 |
| 2019 | 23794 | 8.2e-05 | 7.1e-07 | 0 | 0 |
| Ohio (OH) | 2017 | 367708 | 2.3e-05 | 2e-07 | 2.4e-07 | 2.4e-07 |
| 2018 | 366316 | 4.9e-05 | 4.3e-07 | 0 | 0 |
| 2019 | 364982 | 1.8e-06 | 1.5e-08 | 0 | 0 |
| Oklahoma (OK) | 2017 | 123982 | 8.5e-05 | 7.4e-07 | 2.4e-07 | 2.4e-07 |
| 2018 | 123614 | 4.1e-05 | 3.5e-07 | 0 | 0 |
| 2019 | 123554 | 1.2e-05 | 1.1e-07 | 0 | 0 |
| Oregon (OR) | 2017 | 130676 | 1.2e-05 | 1e-07 | 1.1e-06 | 1.1e-06 |
| 2018 | 131196 | 4.2e-06 | 3.7e-08 | 1e-07 | 1e-07 |
| 2019 | 131696 | 1.5e-05 | 1.3e-07 | 4.7e-08 | 4.7e-08 |
| Pennsylvania (PA) | 2017 | 403282 | 1.2e-05 | 1.1e-07 | 5.2e-07 | 5.2e-07 |
| 2018 | 401596 | 9e-05 | 7.8e-07 | 0 | 0 |
| 2019 | 399732 | 3.8e-06 | 3.3e-08 | 0 | 0 |
| Puerto Rico (PR) | 2017 | 78046 | 0 | 0 | 0.00043 | 4.2e-05 |
| 2018 | 78046 | 0 | 0 | 4.6e-05 | 4.6e-06 |
| 2019 | 78046 | 0 | 0 | 8.7e-06 | 8.6e-07 |
| Rhode Island (RI) | 2017 | 33292 | 1.5e-05 | 1.3e-07 | 2.7e-06 | 2.7e-06 |
| 2018 | 33202 | 8.4e-06 | 7.3e-08 | 0 | 0 |
| 2019 | 33078 | 0 | 0 | 0 | 0 |
| South Carolina (SC) | 2017 | 158354 | 2.9e-05 | 2.5e-07 | 3.8e-07 | 3.8e-07 |
| 2018 | 159502 | 2.6e-05 | 2.3e-07 | 0 | 0 |
| 2019 | 160764 | 1.3e-06 | 1.2e-08 | 0 | 0 |
| South Dakota (SD) | 2017 | 27528 | 0.00067 | 5.8e-06 | 0 | 0 |
| 2018 | 27566 | 0.0017 | 1.5e-05 | 0 | 0 |
| 2019 | 27622 | 8.6e-05 | 7.5e-07 | 0 | 0 |
| Tennessee (TN) | 2017 | 211574 | 3.6e-05 | 3.1e-07 | 2.8e-07 | 2.8e-07 |
| 2018 | 212442 | 1.6e-05 | 1.4e-07 | 0 | 0 |
| 2019 | 213236 | 3e-06 | 2.6e-08 | 0 | 0 |
| Texas (TX) | 2017 | 892342 | 3.8e-05 | 3.3e-07 | 1.8e-06 | 1.8e-06 |
| 2018 | 898152 | 4.5e-05 | 3.9e-07 | 6.1e-08 | 6.1e-08 |
| 2019 | 905372 | 7.2e-06 | 6.2e-08 | 1.4e-08 | 1.4e-08 |
| Utah (UT) | 2017 | 97796 | 0.00016 | 1.4e-06 | 1.2e-06 | 1.2e-06 |
| 2018 | 98934 | 3.1e-05 | 2.7e-07 | 2.8e-07 | 2.8e-07 |
| 2019 | 100104 | 4.5e-05 | 3.9e-07 | 6.2e-08 | 6.2e-08 |
| Vermont (VT) | 2017 | 19690 | 3.8e-05 | 3.3e-07 | 6.1e-06 | 6.1e-06 |
| 2018 | 19588 | 1.4e-05 | 1.2e-07 | 0 | 0 |
| 2019 | 19484 | 0 | 0 | 0 | 0 |
| Virginia (VA) | 2017 | 266914 | 1.2e-05 | 1.1e-07 | 7.8e-07 | 7.8e-07 |
| 2018 | 266706 | 5e-05 | 4.3e-07 | 5.1e-08 | 5.1e-08 |
| 2019 | 266514 | 4.9e-06 | 4.2e-08 | 2.3e-08 | 2.3e-08 |
| Washington (WA) | 2017 | 234108 | 1.4e-05 | 1.2e-07 | 1.9e-06 | 1.9e-06 |
| 2018 | 236042 | 3.5e-06 | 3.1e-08 | 0 | 0 |
| 2019 | 237768 | 4.5e-06 | 3.9e-08 | 0 | 0 |
| West Virginia (WV) | 2017 | 57302 | 4.4e-06 | 3.8e-08 | 5.2e-07 | 5.2e-07 |
| 2018 | 56606 | 9.8e-06 | 8.5e-08 | 0 | 0 |
| 2019 | 55958 | 0 | 0 | 0 | 0 |
| Wisconsin (WI) | 2017 | 182604 | 7e-05 | 6.1e-07 | 6.5e-07 | 6.5e-07 |
| 2018 | 182192 | 5e-05 | 4.4e-07 | 0 | 0 |
| 2019 | 181800 | 2.4e-06 | 2.1e-08 | 0 | 0 |
| Wyoming (WY) | 2017 | 18258 | 9.6e-05 | 8.4e-07 | 3.3e-06 | 3.3e-06 |
| 2018 | 18120 | 6.2e-05 | 5.3e-07 | 0 | 0 |
| 2019 | 18072 | 3.6e-05 | 3.1e-07 | 0 | 0 |

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Table S2. Parameters values for the microsimilation of transfusion-transmitted Zika outcomes

Where distribution parameters are not specified, distribution was fit to the range, using them as 0.025 and 0.975 quantiles except in the case of triangular distriubtion, where the range was used as the minimum and maximum. Parameters without distributions were not varied in sensitiviity analysis. Abbreviations: PSA, probabilistic sensitivity analysis, USD, United States dollars

| **Probability** | **Age, low** | **Value (range); distribution** |
| --- | --- | --- |
| Zika fever |  | 0.184 (0.0959—0.271); Beta |
| Guillain-Barré |  | 0.000257; Beta (42, 1.634e+05) |
| Death from Guillain-Barré |  | 0.0258; Beta (128, 4954) |
| Permanent disability from Guillain-Barré | 0 | 0 |
| 15 | 0.0484 (0.0416—0.0548); Beta |
| 20 | 0.121 (0.104—0.137); Beta |
| 35 | 0.22 (0.208—0.232); Beta |
| 65 | 0.488 (0.471—0.505); Beta |
| Penetrative sex | 0 | 0 |
| 10 | 0.016 (0.00972—0.0273); Beta |
| 15 | 0.214 (0.148—0.31); Beta |
| 20 | 0.532 (0.46—0.621); Beta |
| 25 | 0.765 (0.722—0.83); Beta |
| 30 | 0.727 (0.682—0.785); Beta |
| 40 | 0.624 (0.583—0.681); Beta |
| 50 | 0.448 (0.402—0.503); Beta |
| 60 | 0.397 (0.344—0.465); Beta |
| 70 | 0.282 (0.221—0.36); Beta |
| Transmission from penetrative sex |  | 0.1 (0.01—0.2); Tri |
| Congenital Zika syndrome |  | 0.0343 (0.0095—0.195); Beta |
| Stillbirth after congenital transmissoin |  | 0.07 (0.054—0.084); Tri |
| Recipient pregnant | 0 | 0 |
| 15 | 0.0234 |
| 20 | 0.0573 |
| 25 | 0.0623 |
| 30 | 0.0541 |
| 35 | 0.0303 |
| 40 | 0.00769 |
| 45 | 0 |
| Pregnancy multiplier for PSA |  | 1 (0.2—1.8); Tri |
| Partner pregnant | 0 | 0 |
| 15 | 0.0442 |
| 20 | 0.108 |
| 25 | 0.118 |
| 30 | 0.102 |
| 35 | 0.0574 |
| 40 | 0.0146 |
| 45 | 0 |

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| **Cost (2019 USD)** | **Age, low** | **Value (range); distribution** |
| --- | --- | --- |
| Productivity | 0 | $32,268 |
| 25 | $74,082 |
| 35 | $96,581 |
| 45 | $109,366 |
| 55 | $88,342 |
| 65 | $60,735 |
| 75 | $38,786 |
| Consumption | 0 | $32,039 |
| 25 | $56,457 |
| 35 | $71,198 |
| 45 | $75,387 |
| 55 | $66,212 |
| 65 | $56,268 |
| 75 | $43,181 |
| True positive test result |  | $92 ($76—$108); Tri |
| False positive test result |  | $92 ($76—$108); Tri |
| Zika fever in recipient (hospitalized) |  | $1,358 ($239—$2,477); Gamma |
| Zika fever in partner (non-hospitalized) |  | $109 ($56—$165); Gamma |
| Guillain-Barré |  | $61,676 ($51,001—$72,351); Gamma |
| Permanent disability from Guillain-Barré |  | $38,580 ($30,864—$46,295); Tri |
| Death from Guillain-Barré |  | $72,476 ($57,980—$86,971); Tri |
| Normal delivery |  | $25,386 ($18,803—$28,206); Tri |
| Infant testing |  | $243 ($194—$292); Tri |
| Mother testing |  | $505 ($404—$606); Tri |
| Stillbirth |  | $6,645 ($5,316—$7,973); Tri |
| delivery with congenital Zika syndrome |  | $26,132 ($20,905—$31,358); Tri |
| Lifetime medical costs with congenital Zika syndrome |  | $4,358,764 ($3,487,011—$5,230,517); Tri |

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| **Health state utility** | **Age, low** | **Value (range); distribution** |
| --- | --- | --- |
| Baseline |  | 0.9 (0.8—1); Tri |
| Zika fever, female recipient | 0 | 0.57 (0.4—0.75); Beta |
| 20 | 0.58 (0.44—0.72); Beta |
| 35 | 0.63 (0.52—0.75); Beta |
| 50 | 0.61 (0.48—0.74); Beta |
| 65 | 0.59 (0.37—0.81); Beta |
| Zika fever, male recipient | 0 | 0.5 (0.3—0.7); Beta |
| 20 | 0.59 (0.4—0.77); Beta |
| 35 | 0.58 (0.44—0.71); Beta |
| 50 | 0.55 (0.41—0.68); Beta |
| 65 | 0.54 (0.37—0.71); Beta |
| Guillain-Barré , year 1 |  | 0.76 (0.349—0.987); Beta (3.818, 1.206) |
| Guillain-Barré , year 2 |  | 0.87 (0.243—1); Beta (1.423, 0.2126) |
| Guillain-Barré , years 3-6 |  | 0.99 |
| Zika fever, partner |  | 0.57 (0.54—0.6); Beta |
| Congenital Zika syndrome |  | 0 |

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| **Duration (years)** | **Age, low** | **Value (range); distribution** |
| --- | --- | --- |
| Zika fever, recipient |  | 21 (1.4—66.2); Gamma (1.456, 14.42) |
| Zika fever, partner |  | 7 (2.3—14.2); Gamma (5.201, 1.346) |
| Congenital Zika syndrome |  | 79.8 |

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Table S3. Parameter values for the microsimulation of transfusion-transmitted WNV outcomes

Where distribution parameters are not specified, distribution was fit to the range, using them as 0.025 and 0.975 quantiles except in the case of triangular distriubtion, where the range was used as the minimum and maximum. Parameters without distributions were not varied in sensitiviity analysis. Abbreviations: AFP, acute flacid paralysis, PSA, probabilistic sensitivity analysis, USD, United States dollars; WNV, West Nile virus

| **Probability** | **Age, low** | **Value (range); distribution** |
| --- | --- | --- |
| Immunocompromise in platelet recipient |  | 0.5 (0.4—0.6); Tri |
| Immunocompromise in other recipient |  | 0.25 (0.2—0.3); Tri |
| Relative risk of disease, immunocompromised |  | 2 (1.6—2.4); Tri |
| Clinical disease given WNV transmission |  | 0.25 (0.2—0.3); Tri |
| Disability from WNV fever, age 50+ |  | 0.11 (0.088—0.132); Tri |
| Disability from WNV fever, age under 50 |  | 0.00015 (0.00012—0.00018); Tri |
| Disability from meningitis |  | 0.22 (0.176—0.264); Tri |
| Disability from encephalitis |  | 0.45 (0.36—0.54); Tri |
| Disability from AFP |  | 0.22 (0.176—0.264); Tri |
| Symptomatic patient has WNV fever | 0 | 0.98 (0.784—1.18); Tri |
| 60 | 0.97 (0.776—1.16); Tri |
| 70 | 0.86 (0.688—1.03); Tri |
| Symptomatic patient has encephalitis | 0 | 0.00804 (0.00643—0.00965); Tri |
| 20 | 0.00682 (0.00546—0.00818); Tri |
| 30 | 0.0068 (0.00544—0.00816); Tri |
| 40 | 0.00858 (0.00686—0.0103); Tri |
| 50 | 0.0105 (0.00838—0.0126); Tri |
| 60 | 0.0195 (0.0156—0.0234); Tri |
| 70 | 0.105 (0.0841—0.126); Tri |
| 80 | 0.111 (0.0887—0.133); Tri |
| Symptomatic patient has meningitis | 0 | 0.0114 (0.00914—0.0137); Tri |
| 20 | 0.0124 (0.00994—0.0149); Tri |
| 30 | 0.0119 (0.0095—0.0143); Tri |
| 40 | 0.0101 (0.00811—0.0122); Tri |
| 50 | 0.00798 (0.00638—0.00958); Tri |
| 60 | 0.00819 (0.00655—0.00983); Tri |
| 70 | 0.0273 (0.0218—0.0328); Tri |
| 80 | 0.0218 (0.0175—0.0262); Tri |
| Symptomatic patient has AFP | 0 | 0.00054 (0.000432—0.000648); Tri |
| 20 | 0.00076 (0.000608—0.000912); Tri |
| 30 | 0.00132 (0.00106—0.00158); Tri |
| 40 | 0.00128 (0.00102—0.00154); Tri |
| 50 | 0.00154 (0.00123—0.00185); Tri |
| 60 | 0.00228 (0.00182—0.00274); Tri |
| 70 | 0.00756 (0.00605—0.00907); Tri |
| 80 | 0.00728 (0.00582—0.00874); Tri |
| Death from WNV fever | 0 | 0 |
| 30 | 6e-04 (0.00048—0.00072); Tri |
| 40 | 4e-04 (0.00032—0.00048); Tri |
| 50 | 3e-04 (0.00024—0.00036); Tri |
| 60 | 0.005 (0.004—0.006); Tri |
| 70 | 0.016 (0.0128—0.0192); Tri |
| 80 | 0.082 (0.0656—0.0984); Tri |
| Death from encephalitis | 0 | 0.015 (0.012—0.018); Tri |
| 20 | 0.011 (0.0088—0.0132); Tri |
| 30 | 0.014 (0.0112—0.0168); Tri |
| 40 | 0.041 (0.0328—0.0492); Tri |
| 50 | 0.058 (0.0464—0.0696); Tri |
| 60 | 0.108 (0.0864—0.13); Tri |
| 70 | 0.182 (0.146—0.218); Tri |
| 80 | 0.336 (0.269—0.403); Tri |
| Death from meningitis | 0 | 0.005 (0.004—0.006); Tri |
| 20 | 0.003 (0.0024—0.0036); Tri |
| 30 | 0.004 (0.0032—0.0048); Tri |
| 40 | 0.005 (0.004—0.006); Tri |
| 50 | 0.006 (0.0048—0.0072); Tri |
| 60 | 0.008 (0.0064—0.0096); Tri |
| 70 | 0.045 (0.036—0.054); Tri |
| 80 | 0.157 (0.126—0.188); Tri |
| Death from AFP | 0 | 0 |
| 30 | 0.036 (0.0288—0.0432); Tri |
| 40 | 0.061 (0.0488—0.0732); Tri |
| 50 | 0.086 (0.0688—0.103); Tri |
| 60 | 0.091 (0.0728—0.109); Tri |
| 70 | 0.194 (0.155—0.233); Tri |
| 80 | 0.3 (0.24—0.36); Tri |

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| **Cost (2019 USD)** | **Age, low** | **Value (range); distribution** |
| --- | --- | --- |
| Initial cost, WNV fever |  | $9,426; Gamma (1.795, 3336) |
| Initial cost, meningitis |  | $9,434; Weibull (3.039, 7791) |
| Initial cost, encephalitis |  | $36,621; Pearson5 (2.161, 2.013e+04) |
| Initial cost, AFP |  | $95,125; Invgauss (5.593e+04, 2.223e+04) |
| Five year cost, WNV fever |  | $2,082; Expo (0.001271) |
| Five year cost, meningitis |  | $652; Expo (0.003184) |
| Five year cost, encephalitis |  | $10,302; Expo (0.0001316) |
| Five year cost, AFP |  | $66,632; Weibull (1.263, 6182) |
| Annual productivity | 0 | $32,268 |
| 25 | $74,082 |
| 35 | $96,581 |
| 45 | $109,366 |
| 55 | $88,342 |
| 65 | $60,735 |
| 75 | $38,786 |
| Annual consumption | 0 | $32,039 |
| 25 | $56,457 |
| 35 | $71,198 |
| 45 | $75,387 |
| 55 | $66,212 |
| 65 | $56,268 |
| 75 | $43,181 |

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| **Health state utility** | **Age, low** | **Value (range); distribution** |
| --- | --- | --- |
| Baseline in transfusion survivors |  | 0.9 (0.8—1); Tri |
| Multiplier for WNV fever |  | 0.52 (0.472—0.568); Tri |
| Multiplier for meningitis |  | 0.39 (0.35—0.43); Tri |
| Multiplier for encephalitis |  | 0.19 (0.17—0.21); Tri |
| Multiplier for AFP |  | 0.15 (0.135—0.165); Tri |
| Multiplier for disability caused by WNV fever |  | 0.92 (0.904—0.936); Tri |
| Multiplier for disability caused by meningitis |  | 0.88 (0.856—0.904); Tri |
| Multiplier for disability caused by encephalitis |  | 0.78 (0.736—0.824); Tri |
| Multiplier for disability caused by AFP |  | 0.68 (0.616—0.744); Tri |

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| **Duration (years)** | **Age, low** | **Value (range); distribution** |
| --- | --- | --- |
| Duration of WNV fever |  | 0.0178 (0.0027—0.0328); Tri |
| Duration of meningitis |  | 0.0123 (0.0055—0.0191); Tri |
| Duration of encephalitis |  | 0.0795 (0.0055—0.153); Tri |
| Duration of AFP |  | 0.0959 (0.0055—0.186); Tri |
| Duration of disability |  | 5.5 (4.4—6.6); Tri |

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Table S4. Percent of time intervention part of optimal portfolio across 10,000 probabilistic sensitivity analysis iterations

For all geographic areas not shown, the optimal policy was to use no intervention across all PSA iterations. Table S1 shows the state and territory names coresponding to the STUSPS abbreviations. Abbreviations: ID-, individual donation, MP- minipooled, NAT, nucleic acid testing, PSA, probabilistic sensitivity analysis; WNV, West Nile virus

| **STUSPS** | **2017** | **2018** | **2019** |
| --- | --- | --- | --- |
| AL | WNV ID-NAT, 0.02% WNV MP-NAT, 3.43% |  |  |
| AZ | WNV ID-NAT, 0.35% WNV MP-NAT, 16.41% |  | WNV ID-NAT, 2.38% WNV MP-NAT, 48.07% |
| CA | WNV ID-NAT, 0.1% WNV MP-NAT, 8.55% |  |  |
| CO | WNV ID-NAT, 0.02% WNV MP-NAT, 3.06% | WNV ID-NAT, 1.43% WNV MP-NAT, 34.69% | WNV ID-NAT, 1.23% WNV MP-NAT, 31.77% |
| DC |  | WNV ID-NAT, 2.25% WNV MP-NAT, 47.01% | WNV MP-NAT, 0.09% |
| DE |  | WNV ID-NAT, 0.02% WNV MP-NAT, 2.03% |  |
| IA |  | WNV ID-NAT, 7.13% WNV MP-NAT, 91.75% |  |
| ID | WNV ID-NAT, 0.14% WNV MP-NAT, 10.62% | WNV MP-NAT, 0.62% |  |
| IL |  | WNV ID-NAT, 0.29% WNV MP-NAT, 14.63% |  |
| KS | WNV MP-NAT, 0.22% | WNV ID-NAT, 1.12% WNV MP-NAT, 29.54% |  |
| LA | WNV MP-NAT, 1.76% | WNV ID-NAT, 1.83% WNV MP-NAT, 41.67% |  |
| MA |  | WNV MP-NAT, 0.07% |  |
| MD |  | WNV MP-NAT, 0.08% |  |
| MI |  | WNV MP-NAT, 1.79% |  |
| MN |  | WNV ID-NAT, 0.02% WNV MP-NAT, 3.85% |  |
| MS | WNV ID-NAT, 2.49% WNV MP-NAT, 50% | WNV ID-NAT, 1.42% WNV MP-NAT, 33.94% |  |
| MT | WNV MP-NAT, 0.81% | WNV ID-NAT, 8.23% WNV MP-NAT, 91.75% |  |
| ND | WNV ID-NAT, 11.39% WNV MP-NAT, 88.61% | WNV ID-NAT, 44.56% WNV MP-NAT, 55.44% | WNV MP-NAT, 0.69% |
| NE | WNV ID-NAT, 6.94% WNV MP-NAT, 91.47% | WNV ID-NAT, 18.99% WNV MP-NAT, 81.01% | WNV ID-NAT, 0.02% WNV MP-NAT, 3.92% |
| NJ |  | WNV MP-NAT, 0.05% |  |
| NM | WNV ID-NAT, 0.36% WNV MP-NAT, 16.48% |  | WNV ID-NAT, 0.6% WNV MP-NAT, 21.01% |
| NV | WNV ID-NAT, 3.23% WNV MP-NAT, 59.05% |  | WNV ID-NAT, 0.02% WNV MP-NAT, 3.59% |
| OK | WNV MP-NAT, 1.01% |  |  |
| PA |  | WNV MP-NAT, 1.72% |  |
| PR | Zika ID-NAT, 0.94% Zika MP-NAT, 19.62% | Zika MP-NAT, 0.01% |  |
| SD | WNV ID-NAT, 11.54% WNV MP-NAT, 88.46% | WNV ID-NAT, 29.71% WNV MP-NAT, 70.29% | WNV MP-NAT, 1.08% |
| UT | WNV ID-NAT, 1.93% WNV MP-NAT, 42.71% |  |  |
| WI | WNV MP-NAT, 0.15% |  |  |
| WY | WNV ID-NAT, 0.02% WNV MP-NAT, 2.96% | WNV MP-NAT, 0.06% |  |

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Figure S1. Policy metrics for the optimal portfolio as a function of Zika and WNV prevalence

Panel A calculated as in figure 3. Panels B-F show key performance measures of the optimal policy at each pair of WNV and Zika prevalence values.

