

Individual-based model evaluation of using vaccinated hatchery fish to minimize disease spread in wild fish populations

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Abstract. Although vaccination programs are routinely used in terrestrial environments to protect wild and captive populations against infectious disease, their use in fish populations has been limited to aquaculture/hatchery facilities. A major challenge to enacting a vaccination program for wild fish populations is how to efficiently vaccinate large numbers of susceptible individuals. One possible solution to this dilemma would be vaccinating hatchery-propagated fish prior to their being stocked into infected systems, although the effectiveness of such a program is uncertain. We constructed a spatially explicit individual-based model to evaluate the effectiveness of vaccinating hatchery-propagated fish to protect wild Lake Michigan Chinook salmon *Oncorhynchus tshawytscha* against a disease exhibiting characteristics similar to viral hemorrhagic septicemia genotype IVb. Simulations tracked growth, movement, mortality, maturation, wild reproduction, and disease transmission during a 25-yr time period. Disease states consisted of vaccinated, susceptible, infected, shedding (i.e., infectious), and recovered. Factors that were examined included level of clustering among at-large individuals, infection probability, relationship between viral exposure and mortality, number of stocked individuals, whether recovered individuals could resume viral shedding, and disease initialization status. At an annual stocking level of 2.4 million Chinook salmon, vaccination decreased the percent of the population infected by 23–74% per year depending on the factors evaluated. Doubling the stocking level of vaccinated individuals resulted in similar levels of protection. The largest decrease in percent infected occurred under a condition of low infection probability, high exposure mortality, and high degree of clustering. The protection stemming from vaccination was just slightly smaller under conditions of high infection and high exposure mortality. Complete disease eradication only occurred when recovered individuals could not resume viral shedding. Under such conditions, vaccination sometimes was not even necessary for disease eradication. Our modeling efforts showed that a vaccination program based on immunizing hatchery-propagated individuals prior to stocking may help protect wild fish populations, although disease eradication may be difficult to achieve when recovered individuals can resume shedding viral particles.

Key words: Chinook salmon; disease; fisheries; herd immunity; individual-based model; Lake Michigan; vaccination; viral hemorrhagic septicemia.

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INTRODUCTION

Disease can be a major source of mortality in fish populations, with outbreaks occasionally

resulting in drastic reductions in population abundances (Lafferty et al. 2015). For example, whirling disease, which affects captive and wild salmon populations, has killed upwards of 90%

of salmonid populations in some streams in the western United States (Steinbeck Elwell et al. 2009). In Lake Michigan in the late 1980s and early 1990s, a bacterial kidney disease outbreak reduced biomass of age 3 and older Chinook salmon *Oncorhynchus tshawytscha* by approximately 70% (Tsehaye et al. 2014) with angler catch rates in some areas of the lake decreasing by nearly 85% (Hansen and Holey 2002).

Vaccination programs in terrestrial environments have been used to protect wild and captive populations against disease outbreaks. Perhaps the most familiar terrestrial vaccination program has been that to prevent spread of rabies in central Europe and the eastern United States (Rupprecht et al. 2004). Similar programs have been attempted to protect against classical swine fever (Lange et al. 2012) and have been considered for diseases such as Lyme disease, brucellosis, West Nile virus, and H5N1 avian influenza (Cross et al. 2007). In aquatic systems, however, the use of vaccination programs to protect fish populations has been limited to aquaculture/hatchery facilities. There are numerous challenges to implementing a vaccination program for limiting disease spread in a wild fish population. For one, marine and some freshwater (e.g., Laurentian Great Lakes) fish populations can be very abundant, spread across vast areas, and exhibit complicated movement patterns that may not be fully understood. Additionally, it is uncertain whether herd immunity, which is a necessary precursor for a vaccination program to be effective, can be elicited in an aquatic setting. A recent laboratory experiment demonstrated a herd immunity response in fish against viral hemorrhagic septicemia genotype IVb (VHSV-IVb), although the mechanism for this protective effect was not identified (Standish et al. 2016a). One challenge to implementing a vaccination program in a wild fish population is designing a method for vaccine delivery such that large numbers of susceptible individuals could be immunized. In terrestrial systems, oral delivery by distributing vaccinated bait is presently the method of choice for its efficiency in immunizing large numbers of susceptible individuals in wild populations (Cross et al. 2007). In a wild fish population, antigen destruction in the gut can limit the effectiveness of oral vaccines (Somerset et al. 2005) and designing a bait that wild fish would consume may prove difficult.

Although following a traditional terrestrial model of vaccinating susceptible individuals in at-large populations to prevent disease spread would be difficult to implement in wild fish populations, an alternative approach that might prove effective would be vaccinating hatchery-propagated fish prior to their being stocked into infected systems (Standish et al. 2016a). While fish stocking may not be as widespread as it once was, federal, state/provincial, tribal, and public agencies/groups continue to use stocking to enhance sportfish opportunities and conserve/restore populations at risk. For example, between 1990 and 2010 an average of 15.97 million fish was stocked annually into Lake Michigan (FWS/GLFC 2010). A program designed around the vaccination and release of hatchery-propagated fish would resolve some challenges associated with protecting a wild fish population, namely the ability to vaccinate a large number of susceptible individuals. Nevertheless, there remain questions as to the efficacy of such a vaccination program given some of the other challenges associated with vaccinating fish (e.g., large populations, complex movement strategies).

The purpose of this study was to conduct a model-based evaluation of the potential of vaccinating hatchery-propagated fish as a means to limit disease spread in wild fish populations. We constructed a spatially explicit individual-based model (IBM) based on Chinook salmon abundance and dynamics in Lake Michigan. Individual-based models are considered an effective tool for this type of research because they can capture the emergence dynamics of disease and the spatial structure of infected populations (Grimm and Railsback 2005), which likely will affect vaccination program effectiveness. Individual-based models previously have been used to evaluate disease spread and effectiveness of vaccination programs in humans (Eubank et al. 2004, Perez and Dragicevic 2009, Geard et al. 2015) and wildlife populations (Lange et al. 2012, Rees et al. 2013). We based our simulations on Chinook salmon in Lake Michigan because of the availability of information on the population dynamics and ecology of the species in the system. Some aspects of disease dynamics were based on VHSV-IVb, an emerging sublineage of VHSV with a wide host range that spread throughout the Great Lakes watershed within 5 yr of emergence and caused massive fish

die-offs in several systems (Faisal et al. 2012). The magnitude of the VHSV-IVb outbreak in the Great Lakes prompted numerous investigations into relevant aspects of the disease, such as species-specific susceptibility, mortality, and viral shedding rates, which we utilized for this research. However, we intended our evaluation to be generic so there are disease-dynamic aspects that differ from that of VHSV-IVb. Essentially, we used the computational power of IBMs, the vast body of knowledge on Lake Michigan Chinook salmon population dynamics and ecology, and experimental information on a pathogen that succeeded in invading and spreading across an enormous watershed to explore the potential effectiveness of vaccinating hatchery-propagated fish as a means to improve health status of wild fish.

METHODS

Model description

We describe the IBM used in this research following the updated version of the overview, design, and details protocol (Grimm et al. 2010).

Purpose

The purpose of the IBM was to evaluate the effectiveness of a program designed around the vaccination and release of hatchery-propagated individuals in protecting Lake Michigan Chinook salmon against spread of a viral disease that shared some characteristics with VHSV-IVb.

Entities, state variables, and scales

Lake Michigan was represented by a grid consisting of 1.8 km² cells (Fig. 1). Associated with each cell was a unique identifier, Cartesian coordinates, mean depth (m), and daily temperature (°C). Superindividuals (SIs) representing multiple Chinook salmon with similar life-history characteristics were tracked to reduce computation time (Scheffer et al. 1994). Models were run for 25 yr. The maximum age of Lake Michigan Chinook salmon is generally around 5 yr and fish die after spawning so 25 yr was deemed a sufficient timeframe for evaluating vaccination benefits on the at-large population. Each SI had state variables that included a unique identifier, number of individuals represented, length (cm), weight (kg), maturity status, age, sex, infection

state (susceptible, infected, shedding, recovered, or vaccinated), various information related to disease states (e.g., time to death, time to shed, time to recovery, shedding rate in plaque forming units [PFUs] exuded, number of individuals to remove from a SI, a counter that kept track of transition among infection states), location, and two variables that determined a SI's grow rate (a lifetime proportion of maximum consumption and an age-specific maximum consumption value).

Process overview and scheduling

The model ran on a daily time step in the following order: update cell temperatures, randomize individuals before daily processes, and update individual state variables (Fig. 2). For each SI, five processes occurred daily in the following order: natural mortality, fishing mortality, update disease status, movement, and growth. Several additional processes occurred on select days of the year: updating maturation status and production of new individuals on day 241, and age-0 fish (both hatchery and naturally produced) emerging from rivers or hatcheries and entering the at-large population on days 121–166 (depending on natal river or stocking location).

Design concepts

Basic principles.—The model used individual-based theory (Grimm and Railsback 2005) to track the emergence of disease in Chinook salmon. Disease dynamics were represented with a susceptible-exposed-infectious-recovered (SEIR)-type epidemiology submodel, with some modifications to account for VHSV-IVb dynamics. Movement of fish was probabilistically determined toward cells that optimized temperature occupancy with a tendency to move northward during summer and southward during winter. Simulated scenarios were designed to determine the effectiveness of a vaccination program under varying infection probabilities, relationships between viral exposure and disease mortality, degree of population clumping, and stocking level.

Emergence.—Chinook salmon population dynamics emerged from interactions between disease spread and individual behaviors of mortality, movement, growth, maturation, and reproduction. Basic processes, like mortality, growth, and movement probability, were derived from

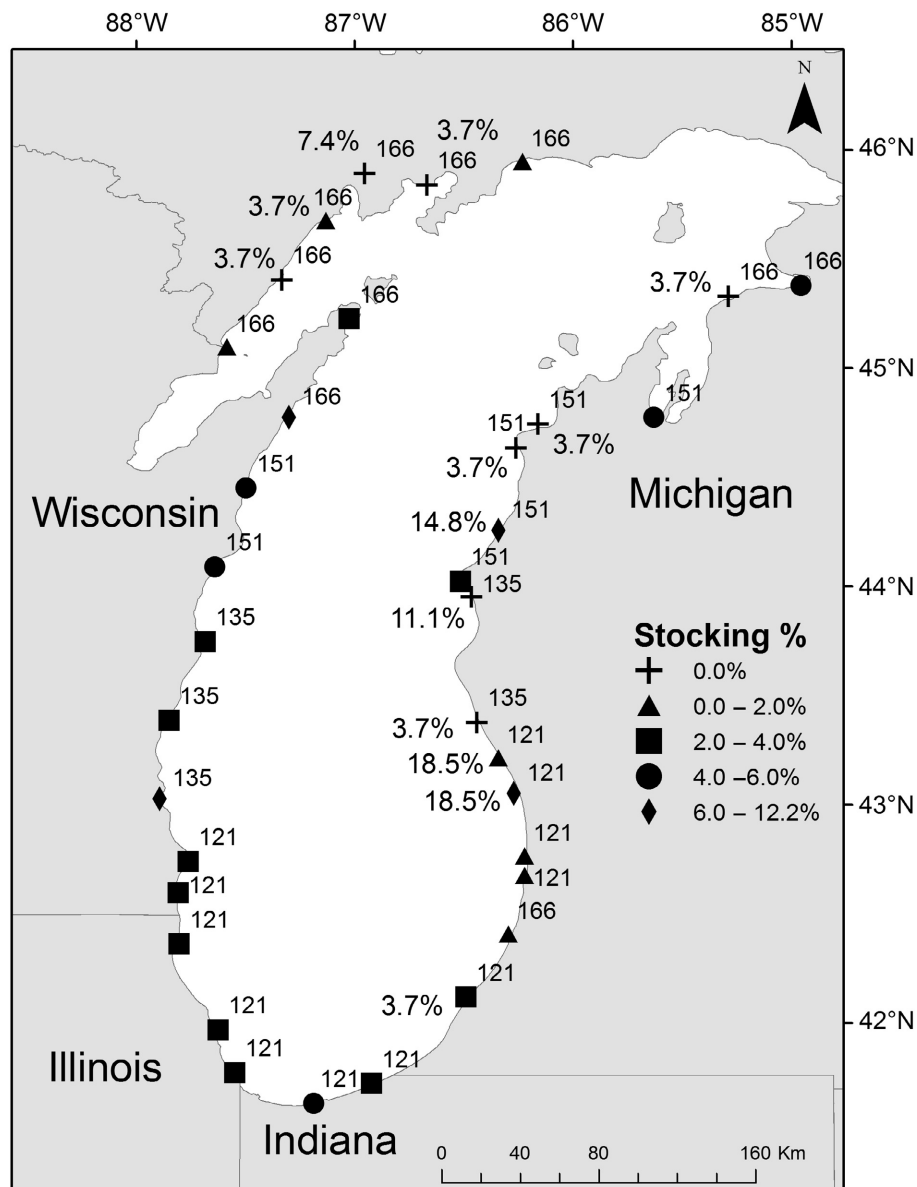


Fig. 1. Map of Lake Michigan, which was the spatial basis for this research showing hatchery release locations and wild fish production sites. Different symbols indicate the percentage of stocked fish that were planted at each site. Integer values indicate date of stocking or emergence from the river. Percentage values next to some sites indicate the percentage of wild fish production assumed from that site.

empirical relationships with built-in stochasticity. The epidemic course of the disease emerged from within individual infections, vaccination program being evaluated, and individual movements.

Adaptation.—Fish made decisions on movement, with a greater probability of movement toward more optimal cells based on thermal

preferences and north and south movement during summer and winter months, respectively.

Objectives.—A fish's objective was to move toward a more thermally suitable environment. Immunity to disease was not a direct function of movement; however, where a fish moved to could result in fish congregation, which could increase viral exposure.

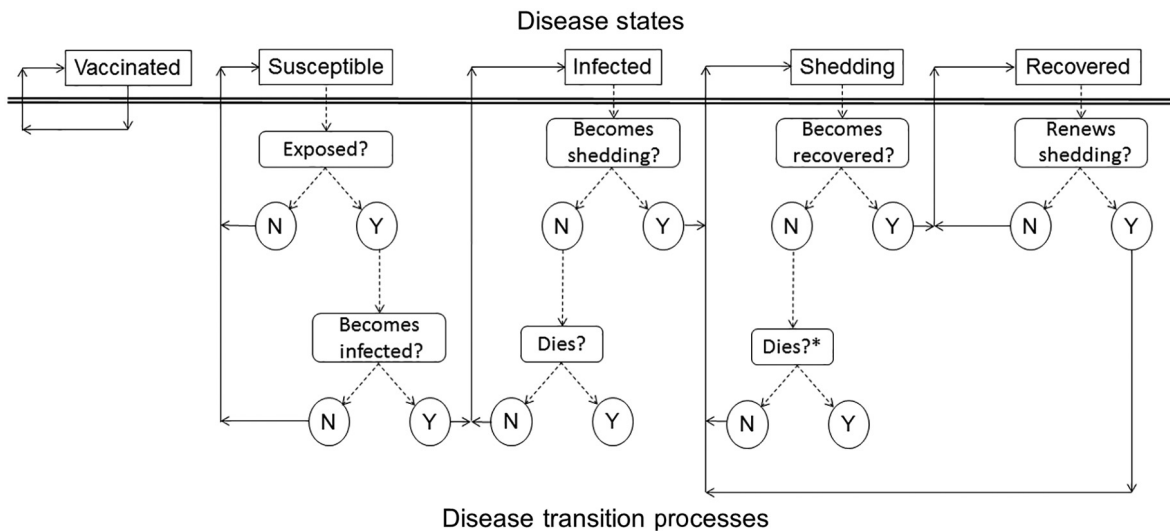


Fig. 2. Flow diagram depicting disease states and showing processes how individuals transitioned between states. When individuals died in the infected or shedding state, their status was no longer updated. Shedding individuals that transitioned from the recovered state could not die from infection. The asterisk indicates that recovered fish that transitioned back to shedding were not allowed to die.

Learning.—Fish did not learn in this model.

Sensing.—Fish were assumed to sense temperature for daily movement.

Interaction.—Fish interacted directly via disease transmission.

Stochasticity.—Stochasticity was incorporated in multiple processes, including (1) determination of annual natural and fishing mortality rates and whether individuals died from natural or fishing causes on any given day, (2) weight at age for age-1 and older individuals in the first modeled year, (3) lengths of age-0 fish originating from stocking or wild production, (4) age-specific maximum annual consumption rates for individuals, (5) life-long proportion of the maximum annual consumption rate that individuals consumed at, (6) movement, (7) disease transmission, (8) whether and when an infected fish would die from the disease, (9) shedding rate in PFUs of infected individuals and length of shedding, and (10) whether a recovered individual could resume shedding.

Collectives.—Fish occupying the same grid cell on the same day were assigned to individual groups that determined contact for disease spread. For infection to occur, a fish needed to occupy the same cell and be assigned to the same group as a shedding individual to be considered to have come into contact with the virus. The number of

groups (1, 10, 20, or 100) that fish were divided into daily was a factor that was explored in this research to determine its influence on disease spread and vaccination program effectiveness.

Observations.—For each simulation, total abundance; abundance in each disease state; numbers of fish that died due to natural, fishing, or disease-related mortality; number of fish that became infected; and number of recovered individuals that resumed shedding were recorded every 30 d for each year and age.

Initialization

The model was initialized with 50,000 SIs randomly distributed throughout the lake representing a population of approximately 9.4 million fish, which was the estimated total abundance of Lake Michigan Chinook salmon in 2014 based on the assessment model of Tsehaye et al. (2014). A 1:1 sex ratio was assumed. Initialized age composition corresponded to the estimated age composition of Lake Michigan Chinook salmon in 2014 based on the assessment model of Tsehaye et al. (2014; Table 1). Weights of individuals were randomly generated from a normal distribution with age-specific means and standard deviations based on observed weights at age from recreational angler creel surveys conducted by the Michigan

Table 1. Assumed parameter values by age, including annual maximum consumption (CM), gross conversion efficiency (GCE), fishing mortality (F), natural mortality (M), maturation (Mat.), weight (kg) in the initial year (W), and age composition in the initial year (Composition proportion), for modeling growth, mortality, maturation, and weight at age and age composition at model initialization.

Parameter	Age 0	Age 1	Age 2	Age 3	Age 4	Age 5
CM Normal dist. Mean	3.37	10.75	28.90	39.86	67.26	67.26
CM Normal dist. stand. dev.	1.01	3.22	8.67	11.96	20.18	20.18
GCE value	0.243	0.224	0.152	0.075	0.030	0.030
F Normal dist. mean	0.000	0.027	0.150	0.499	0.579	0.57
F Normal dist. stand. dev.	0.000	0.004	0.0237	0.079	0.092	0.092
M Normal dist. mean	0.700	0.391	0.460	0.118	0.118	0.118
M Normal dist. stand. dev.	0.000	0.094	0.372	0.019	0.019	0.019
Mat. Beta parameter	NA	0.383	0.298	0.213	0.128	NA
Mat. Alpha parameter	NA	9.871	9.112	6.732	0.553	NA
W Normal dist. mean	0	0.78	2.24	4.28	6.61	9.067
W Normal dist. stand. dev.	0	0.05	0.29	0.51	0.72	1.00
Composition proportion	0.553	0.152	0.246	0.045	0.004	2.049E-04

Notes: Parameter values were informed based on assessment results from Tsehaye et al. (2014). NA indicates parameter values for that particular age were not needed.

Department of Natural Resources (Table 1). In simulations where disease was assumed to occur, initialization of population status was as follows: 10% of the population was infected, 40% was recovered, and 50% was susceptible to infection. As part of a sensitivity analysis, we conducted simulations with an alternative population status initialization to see how results were affected by this assumption (see *Sensitivity scenarios* section).

Input data

Parameter values used in various submodel routines described below were read into the model. The Lake Michigan grid file that included Cartesian coordinates, unique cell identifiers, and mean depth (m) was also a model input. Daily temperature values for each Lake Michigan grid cell were a model input and were based on a modified temperature dataset produced from a Lake Michigan thermodynamic model (D. Beletsky, University of Michigan, *unpublished data*). The thermodynamic model produced temperatures every 6 h at 20 depth levels. To create daily temperatures for our model, we averaged temperature data over each day for the upper 20 m of the water column.

Submodels

Growth.—Weights at age for age-1 and older fish at initialization were randomly generated

from a normal distribution with age-specific means and standard deviations (Table 1). For age-0 fish, initial lengths (mm) were randomly generated from uniform distributions with lower and upper bounds of 65 and 91 mm for wild-produced fish (Krueger et al. 2011) and 73 and 111 mm for hatchery-produced fish (J. Jonas, Michigan DNR, *unpublished data*). Weights (kg) of age-0 fish were then calculated as

$$W_i = 4.0E - 10 \times L_i^{3.7165}$$

where i indexes the i -th SI, W is weight, and L is length. Increases in weight were modeled as

$$W_{i,t+1} = W_{i,t} + (p_i \times CM_{i,a} \times GCE_a)$$

where t indexes time period, a indexes fish age, CM is the daily maximum consumption rate, p is the lifetime-specific proportion of maximum consumption at which an SI consumes, and GCE is growth conversion efficiency. For each SI at each age, an annual maximum consumption rate was randomly generated from a normal distribution with age-specific means and standard deviations (Table 1). Annual maximum consumption rates were converted to daily rates by dividing by 365 for age-1 and older fish and 214 for age-0 fish. A uniform distribution with lower and upper bounds of 0.6 and 1.0 was used to randomly generate lifetime-specific proportion of maximum consumption at which a SI consumed.

Age-specific gross conversion efficiencies, which measures an individual's ability to convert ingested biomass into new tissue, were assumed values based on estimates from Tsehaye et al. (2014; Table 1).

Fishing and natural mortality.—For each SI, an annual instantaneous natural mortality rate was randomly generated at each age from a normal distribution with age-specific means and standard deviations (Table 1). The age-specific means and standard deviations were calculated from the estimated annual natural mortalities of Lake Michigan Chinook salmon from 2005 to 2014 based on the assessment model of Tsehaye et al. (2014). Randomly generated annual values were converted to daily values by dividing by 365 for age-1 and older fish and 214 for age-0 fish. Daily finite rates were calculated from daily instantaneous rates as

$$v_{i,t} = 1 - \exp^{-M_{i,t}}$$

where v is the daily finite rate and M is the daily instantaneous rate. The total number of individuals removed from a SI due to natural mortality was randomly generated from a binomial distribution where the sample size of the distribution was the number of individuals the SI represented at that time and the probability was the assigned daily finite natural mortality rate.

Deaths due to fishing were generated similarly to deaths due to natural mortality but with some slight modifications. An apical monthly instantaneous fishing mortality rate was randomly generated at each age from a normal distribution with age-specific means and standard deviations (Table 1). The age-specific means and standard deviations were calculated from the estimated apical monthly fishing mortalities of Lake Michigan Chinook salmon from 2005 to 2014 based on the assessment model of Tsehaye et al. (2014). Monthly fishing mortalities that each SI would experience was calculated as the product of the randomly generated apical monthly fishing mortalities and the monthly relative proportion of fishing that was calculated to occur for Lake Michigan Chinook salmon based on the assessment model of Tsehaye et al. (2014). These monthly instantaneous fishing mortalities were converted to daily finite rates. The total number of individuals removed from a SI due to fishing mortality was randomly generated from a binomial

distribution where the sample size of the distribution was the number of individuals the SI represented at that time and the probability was the assigned daily finite fishing mortality rate.

Disease transmission and death from disease.—Our model included five disease states: susceptible, infected (but not yet shedding the virus, i.e., exposed), shedding (infected and shedding the virus, i.e., infectious), recovered with the possibility of reshedding, and vaccinated (Fig. 2). Infection, which could occur at any point during the year, occurred by susceptible SIs contacting a shedding SI. By contacting, we mean that fish occupied the same Lake Michigan grid cell on the same day and were assigned the same cluster (see *Collective design concept*). The probability of a susceptible SI becoming infected given that it contacted a shedding SI was a factor that was evaluated as part of our simulations (see *Simulation scenarios*).

At time of infection, probability of death was calculated based on level of viral exposure, which was a function of the sum PFU shedding rate of all shedding SIs in the same group and grid cell as the newly infected fish and the ratio of vaccinated-to-susceptible SIs. Two probability-of-death functions were considered as part of our research (see *Simulation scenarios*). If the cluster to which an infected individual was assigned contained more vaccinated than infected individuals, the probability of death was reduced by 50%, which was approximately the reduction in mortality rate to VHSV-IVb found in the experimental herd immunity study of Standish et al. (2016a). The length of time until death occurred was randomly generated from a uniform distribution with lower and upper bounds of 6 and 28 d, which is similar to the time to death for VHSV-IVb-infected individuals observed by Kim and Faisal (2010b). The total number of individuals removed from a SI due to infection mortality was randomly generated from a binomial distribution where the sample size of the distribution was the number of individuals the SI represented at that time and the probability was the calculated probability of death based on exposure and the function under consideration.

The length of time before infected SIs transitioned to shedding SIs (Fig. 2) was randomly generated from a uniform distribution with lower and upper bounds of 1 and 7 d, which was based on the amount of time until VHSV-IVb-infected

individuals began shedding virus particles observed by Kim and Faisal (2010b) and Standish et al. (2016b). The length of time that fish remained in the shedding state was randomly generated from a uniform distribution with lower and upper bounds of 14 and 84 d, which was based on observed VHSV-IVb shedding duration from the research by Kim and Faisal (2012). Shedding SIs were randomly assigned one of five shedding levels (probability of being assigned this shedding level): 100 PFUs (4.11%), 1000 PFUs (13.70%), 10,000 PFUs (30.14%), 100,000 PFUs (39.73%), and 1,000,000 PFUs (12.33%). We assumed widely varying shedding rates based on observed shedding rates of fish infected with VHSV-IVb (Kim and Faisal 2012, Standish et al. 2016b).

After the shedding period was completed, SIs transitioned into the recovered state (Fig. 2). Once recovered, SIs had a low probability of transitioning back to a shedding state (Fig. 2), which is similar to what was found for VHSV-IVb by Kim and Faisal (2012). Recovered individuals that transitioned back to the shedding state could not die from infection, but otherwise their processes were the same as newly shedding SIs. Probability of recovered SIs transitioning back to a shedding state was an exponentially decreasing function

$$\pi_r = 0.05 \times \exp(-0.002 \times r)$$

where r is the number of days since recovery from initial infection. On each day, whether a recovered SI transitioned back to a shedding state was randomly generated from a Bernoulli distribution with the probability parameter set equal to π_r .

Movement.—Past research has reported a variable range of daily movement distances for Pacific salmonids *Oncorhynchus* spp. in open water. Using a predicted swimming speed of 1 body length/second, a 60-cm sockeye salmon *Oncorhynchus nerka* was predicted by Brett (1983) to be capable of moving 52 km/day. Quinn (2005) reported daily movements of 16–25 km/day for *Oncorhynchus* spp., while Haynes et al. (1986) observed daily movements of 3.2 km/day for 38-cm steelhead *Oncorhynchus mykiss* in Lake Ontario. For our model, we limited the maximum distance a SI could move to 4 km/day for age-0 fish and 12 km/day for age-1 and older SIs. All cells within

the range of a SI's movement distance, including its current cell, were assessed for temperature. A cell's thermal value (TV_k) was assigned based on a simple scale of 1 (outside the range of a fish's bounds for growth), 2 (in the range of a fish's bounds for growth), or 4 (inside the range of the optimal temperature for growth). For Chinook salmon, the bounds for growth are 4.5–19.1°C, while the bounds for optimum growth are 10.0–15.5°C (McCullough 1999). In addition, cells north of a SI's current location were multiplied by 2 between days 90 and 240, while cells south of a SI's current cell were multiplied by 2 the rest of the year to invoke a directional north-to-south and south-to-north movement, respectively. The probabilities of a SI moving to cell k within its movement range were then calculated as

$$pr_k = \frac{TV_k}{\sum_{k=1} TV_k}$$

The exact cell that a SI moved to within its movement range was randomly generated from a categorical distribution where the categories corresponded to the cells to which an individual capable of moving and the category probabilities were set equal to pr_k .

Maturation.—Probability of maturing on day 240 depended on fish age and weight. For age-0 fish, the probability of maturing was assumed to be 0%, while for age-5 fish the probability of maturing was 100% regardless of size. For fish ages 1–4, the probability of maturation was calculated as

$$\theta_{i,a} = \frac{1}{1 + e^{(-\beta_i \times (W_i - \alpha_i))}}$$

where θ is the probability of the i -th individual that is age a maturing, α and β are age-specific parameters of the function (Table 1), and W_i is the weight of the i -th individual (Tsehaye et al. 2014). On day 240, whether a SI matured was randomly determined from a Bernoulli distribution with the probability parameter set equal to $\theta_{i,a}$. All maturing and reproducing individuals were assumed to die after spawning (Tsehaye et al. 2014).

Reproduction.—Wild reproduction from each SI was a product of SI biomass (the product of SI weight and the number of individuals an SI represented at time of spawning) and the number of age-0 fish produced per kilogram of spawning

Chinook salmon, which was randomly generated annually for all spawning SIs from a normal distribution with a mean and standard deviation of 3.0 and 1.0 fish, respectively, and a minimum value of 0.5 fish per kilogram. The means and standard deviations for the number of age-0 fish produced per kilogram of spawning Chinook salmon were based on estimated values for Lake Michigan from the assessment model of Tsehaye et al. (2014). Total wild reproduction was the sum of the wild reproduction of each mature SI. A 1:1 sex ratio was assumed for wild-reproduced fish. Wild-reproduced fish were initially allocated to 15 grid cells corresponding to rivers where Chinook salmon in Lake Michigan are known to reproduce (Fig. 1). Allocation was proportional based on estimated levels of wild production from these rivers (E. Rutherford, NOAA Great Lakes Environmental Research Laboratory, *unpublished data*). The date that each wild-produced SI entered the lake varied by river of origination (Fig. 1).

The number of hatchery fish stocked into the lake, and whether or not stocked fish were vaccinated, were factors that were evaluated as part of our simulations (see *Simulation scenarios*). Fish were assumed to be stocked in 27 locations throughout the lake (Fig. 1). Stocking allocation was based on actual stocking history for Lake Michigan. Once assigned to a river, fish were held at the river mouth cell until hatch day, which was dependent on the assigned river and was later in the season for northerly rivers (days 121–166). Prior to hatch, fish did not interact with other fish or experience any growth, mortality, or movement. After hatch, fish were treated the same as naturally produced fish for growth, mortality, movement, and disease unless fish were vaccinated.

Simulation scenarios

An initial calibration scenario was performed assuming an annual stocking level of 2.4 million fish but without any disease in the system. The purpose of the calibration scenario was to establish expected population abundance to which abundances from other simulation scenarios could be compared. The calibration scenario was also used to determine whether simulated fish growth was comparable to observed Lake Michigan Chinook salmon growth and whether

dispersal throughout the lake during the course of the year was similar to current understanding of Lake Michigan Chinook salmon movement (Adlerstein et al. 2008).

Baseline simulations evaluated the following factors in a fully crossed design: infection probability (two levels), probability of death due to exposure (two functions), level of clustering (four levels), and whether or not stocked fish were vaccinated (two levels). All baseline simulations assumed a stocking level of 2.4 million fish, which was the approximate number of Chinook salmon stocked in Lake Michigan in 2014. When stocked fish were vaccinated, vaccination was assumed to be 100% effective throughout the life span of a fish.

The two infection probability levels that we evaluated were 10 (low infection) and 65% (high infection), which was based on the range of low and high susceptibilities for Great Lakes fishes to VHSV-IVb based on the research of Kim and Faisal (2010b, c). The two probability-of-death functions were

$$m_i = 11.313\% \times \log_e(\text{PFU}_i) - 35.922\%$$

for high scenarios (hereafter high exposure mortality) and

$$m_i = 0.7531\% \times \log_e(\text{PFU}_i) - 3.8276\%$$

for low scenarios (hereafter low exposure mortality), where PFU_i is the virus exposure for the i -th SI, calculated as the sum of the PFUs shed by SIs residing in the same cell and cluster exuded.

The four levels of clustering that were evaluated as part of this research were 1 group (high clustering), 10 groups (medium clustering), 20 groups (low clustering), and 100 groups (extra low clustering). Under a 1-group (high cluster) scenario, all SIs located within a 1.8 km² cell on a particular day were assumed to be in close enough contact that if at least one infected or shedding SI was located in the cell any susceptible SI could get infected. Conversely, under a 10-group (medium cluster) scenario, all SIs within a 1.8 km² cell on a particular day were randomly allocated to one of ten clusters. For a susceptible SI in a cluster to have a chance of being infected, a shedding SI would also have to be allocated to that cluster. Allocation to clusters on any particular day was independent of allocations on previous days.

Sensitivity scenarios

In addition to the calibration and baseline simulations, three sensitivity analyses were explored under a high (65%) infection probability scenario to determine how efficiency of a vaccination program changed under alternative conditions. First, simulations were conducted to explore the effects of doubling the stocking rate to 4.8 million fish, which was the average number of Chinook salmon stocked in Lake Michigan between 1990 and 2014. Sensitivity simulations were additionally conducted under an assumption that recovered individuals could not resume shedding the virus. Finally, we explored how the initial disease states in the model impacted the simulation results by altering the initial disease states to 90% susceptible, 5% shedding, and 5% recovered. Sensitivity analyses were only conducted.

Performance metrics

The spatially explicit IBM was coded in FORTRAN (FORTRAN code for the IBM is available for download from figshare <https://doi.org/10.6084/m9.figshare.5794668>), and simulations were performed on Michigan State University High Performance Computing Clusters. A total of 50 iterations were conducted for each investigated scenario. For the purpose of calibration with Chinook salmon abundance estimates from Tsehaye et al. (2014), abundances at the start of the year (day 1) were calculated. We additionally calculated total population abundance on day 240, annual median percent of the population infected (hereafter median percent infected), and annual median percent disease deaths (hereafter median percent deaths). Median percent infected (IR) for scenario j , year k , and iteration l was calculated as

$$\text{IR}_{j,k,l} = 100 \times \left(\frac{\text{Inf}_{j,k,l}}{N_{j,k,l}^1} \right)$$

where $\text{Inf}_{j,k,l}$ is the total number of fish infected for scenario j , year k , and iteration l , and $N_{j,k,l}^1$ is the initial total abundance on day 1 for scenario j , year k , and iteration l . Median percent disease deaths (MR) for scenario j , year k , and iteration l was calculated as

$$\text{MR}_{j,k,l} = 100 \times \left(\frac{D_{j,k,l}}{N_{j,k,l}^1} \right)$$

where $D_{j,k,l}$ is the total number of individuals that died due to disease for scenario j , year k , and iteration l . For each metric, the median value for the last 10 yr for each iteration was used as the actual performance metric so that results were not affected by initialization conditions.

For evaluating the effects stemming from a vaccination program, we examined differences in means of performance metrics averaged across all iterations between unvaccinated and vaccinated simulations under the same infection probability, exposure mortality, and clustering level conditions. For total population abundance on day 240, we calculated the relative difference in simulation means

$$\text{NRD}_j = 100 \times \left(\frac{\sum_l \ddot{N}_{j[\text{unvac}],l}^{240}/50 - \sum_l \ddot{N}_{j[\text{vac}],l}^{240}/50}{\sum_l \ddot{N}_{j[\text{vac}],l}^{240}/50} \right)$$

where $\ddot{N}_{j[\text{vac}],l}^{240}$ is the median abundance on day 240 over the last 10 yr for iteration l for scenario j assuming stocked individuals were vaccinated, and $\ddot{N}_{j[\text{unvac}],l}^{240}$ is the median abundance on day 240 over the last 10 yr for iteration l for scenario j assuming stocked individuals were not vaccinated. For annual median percent infected and annual median percent disease deaths, we calculated actual difference in simulation means between vaccinated and unvaccinated simulations

$$\text{IRD}_j = \sum_l \ddot{\text{IR}}_{j[\text{unvac}],l}/50 - \sum_l \ddot{\text{IR}}_{j[\text{vac}],l}/50$$

$$\text{MRD}_j = \sum_l \ddot{\text{MR}}_{j[\text{unvac}],l}/50 - \sum_l \ddot{\text{MR}}_{j[\text{vac}],l}/50$$

where $\ddot{\text{IR}}_{j[\text{vac}],l}$ and $\ddot{\text{MR}}_{j[\text{vac}],l}$ are the median percent infected and median percent disease deaths, respectively, over the last 10 yr for iteration l for scenario j assuming stocked individuals were vaccinated, and $\ddot{\text{IR}}_{j[\text{unvac}],l}$ and $\ddot{\text{MR}}_{j[\text{unvac}],l}$ are the median percent infected and median percent disease deaths, respectively, over the last 10 yr for iteration l for scenario j assuming stocked individuals were not vaccinated. We used actual differences rather than relative differences for the percentage of the population infected and dying due to disease because these metrics were already expressed as percentages.

RESULTS

Calibration simulation

Simulations without disease produced abundance levels at the start of the year that were comparable to assessment model estimates from Tsehaye et al. (2014). At a stocking level of 2.4 million fish, abundance at the start of the year varied between 6.4 million and 8.3 million, whereas the assessment model of Tsehaye et al. (2014) predicted estimates between 7.8 and 8.6 million under that stocking level based on recent dynamics of the Chinook salmon population in Lake Michigan. Total abundance on day 240 prior to spawning averaged 4.8 million fish under a stocking level of 2.4 million fish. Predicted weights at age ranged from 0.19 to 1.5 kg for age-0 fish, 0.8–5.2 kg for age-1 fish, 2.1–11.7 kg for age-2 fish, 3.3–15.4 kg for age-3 fish, and 4.4–17.2 kg for age-4 fish. Conversely, observed weights at age from creel surveys ranged from 0.2 to 5.7 kg for age-1 fish, 0.5–12.8 kg for age-2 fish, 0.7–14.2 kg for age-3 fish, and 2.4–14.5 kg for age-4 fish (T. Kolb, unpublished

data). Similar to what was reported by Adlerstein et al. (2008), the spatially explicit IBM produced longitudinal differences in Chinook salmon densities at different points of the year with clustering in the southern end of the lake around days 60–90 and clustering in the more northern part of the lake around days 210–240 (Appendix S1: Fig. S1).

Baseline simulations

Examination of disease progression across the simulation timeframe showed that within a few years of model initialization, disease status became relatively stable (e.g., Figs. 3, 4). These results confirmed that 25 yr was a long-enough time period for evaluating disease effects and the benefits stemming from a vaccination program designed around the release of hatchery-propagated fish for the conditions assumed in our spatially explicit IBM. For all performance metrics, variability in model results within a simulation scenario was generally low (Figs. 5–7).

For high infection probability and high exposure mortality scenarios, mean abundance of Chinook

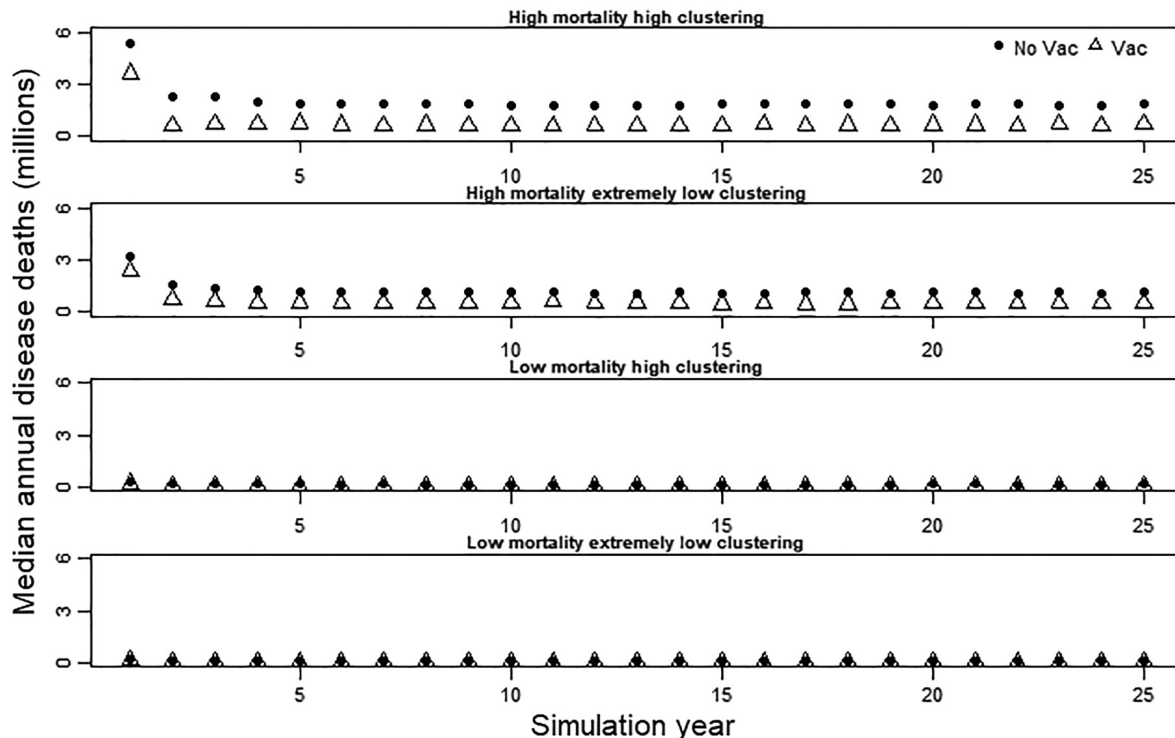


Fig. 3. Median annual disease deaths (millions) by simulation year for select high infection probability scenarios averaged over the 50 iterations conducted for the scenarios.

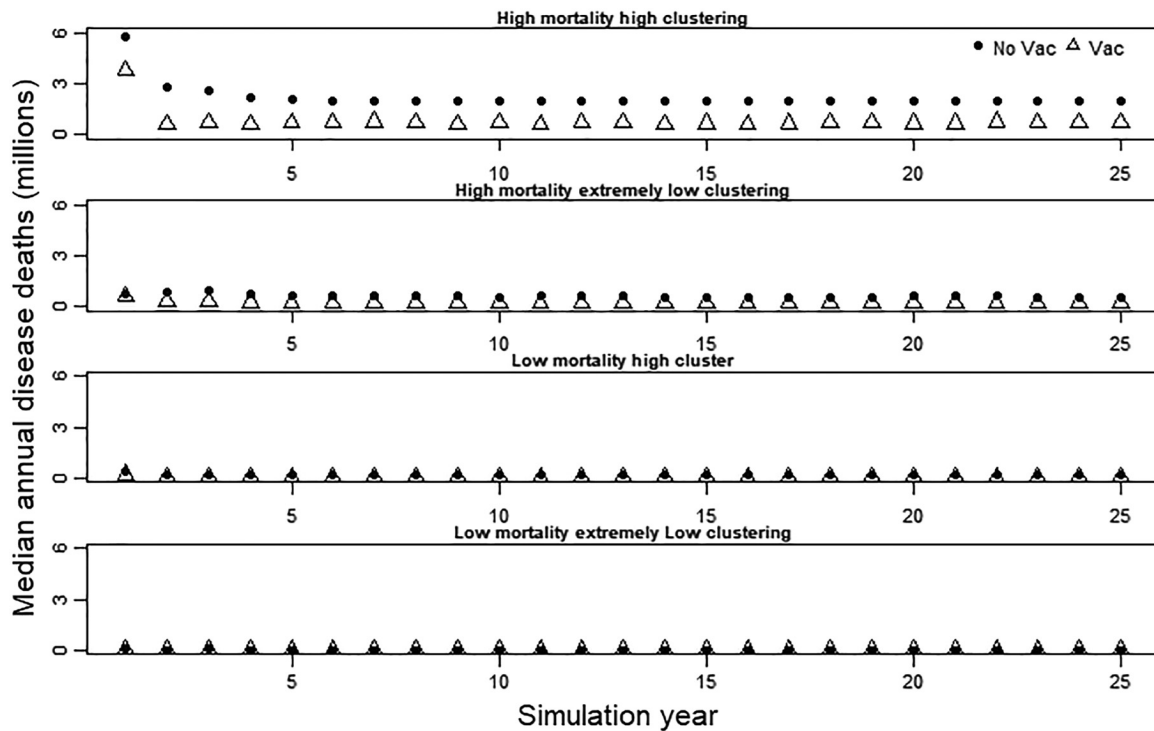


Fig. 4. As in Fig. 3 except for select low infection probability scenarios.

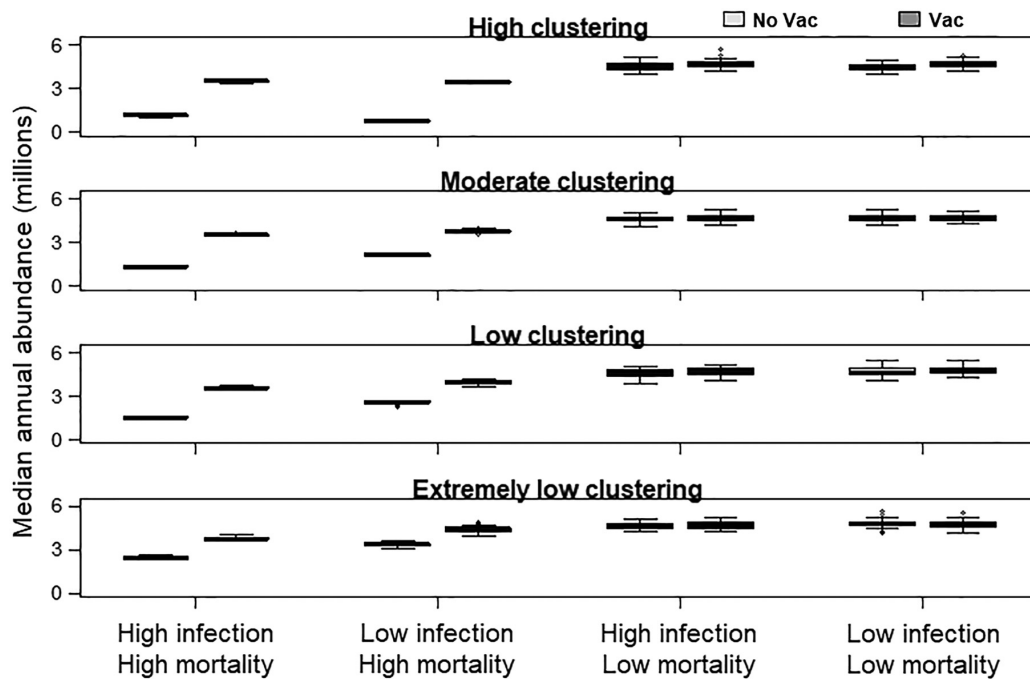


Fig. 5. Median Chinook salmon abundance (millions) on day 240 of the simulation year across all scenarios (median calculated from the last 10 yr of model runs). For each boxplot pair, the left boxplot shows results for scenarios without vaccination, while the right boxplot shows results for scenarios with vaccination.

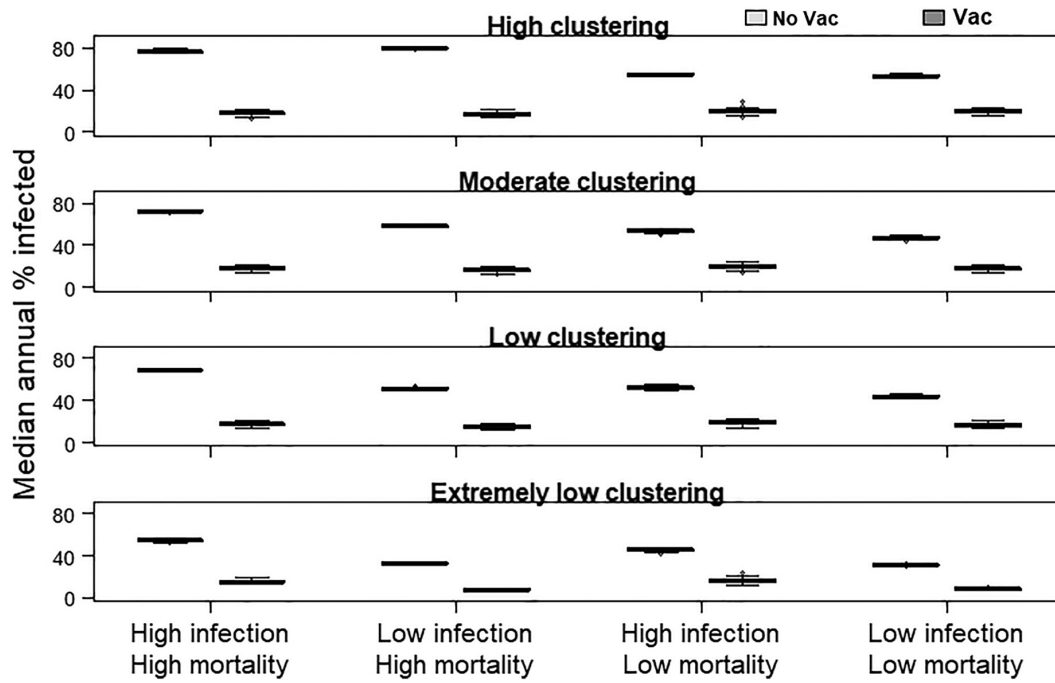


Fig. 6. As in Fig. 5 except results are median percent infected (%) at the end of the simulation year across all scenarios (see text for description for how percent infected was calculated).

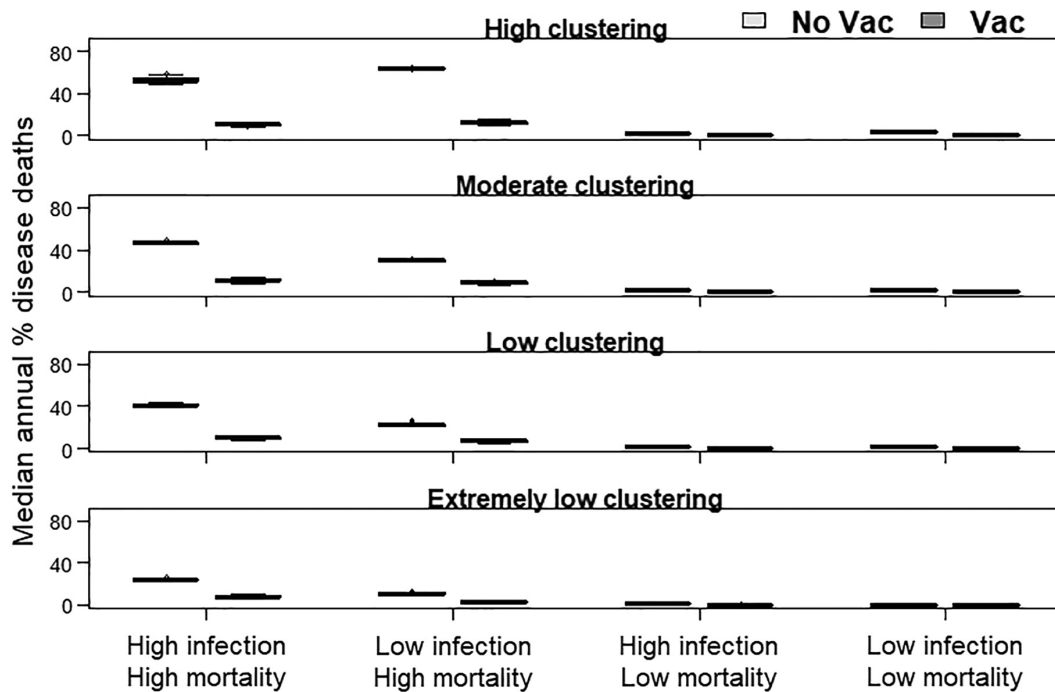


Fig. 7. As in Fig. 5 except results are median deaths (%) due to disease at the end of the simulation year across all scenarios (see text for description for how mortality rate due to disease was calculated).

salmon varied between 1.15 and 2.46 million fish in the absence of vaccination depending on assumed clustering level, with abundance inversely related to the clustering level (i.e., high clustering led to lower abundances; Fig. 5). Without vaccination, mean percent infected ranged from 54% to 76% per year (Fig. 6) and median percent disease deaths ranged from 24% to 52% per year (Fig. 7) across the clustering levels with infection rate and mortality rate positively related to clustering level. With vaccination, median abundance increased anywhere from 55% to 208% compared to abundances in the absence of vaccination, with changes in abundance positively related to clustering level (Table 2, Fig. 5). Conversely, median percent infected declined by 39% to 59% and median percent disease deaths declined by 16% to 42% when stocked fish were vaccinated compared to when stock fish were not vaccinated with the largest decreases occurring under the high clustering scenario (Table 2, Figs. 6, 7).

For low infection probability and high exposure mortality scenarios, the assumed clustering level had a large effect on performance metrics. Without vaccination, average abundance decreased to 0.76 million fish under a high clustering assumption (Fig. 5). This decrease in abundance was even greater than what was observed for the high

infection probability and high exposure mortality at the same clustering level. Simulation-average median percent infected and percent disease deaths were around 79% and 63% per year, respectively (Figs. 6, 7), both of which were greater than what was observed for the high infection probability and high exposure mortality scenario. Under the other clustering levels, simulation-averaged abundance ranged from 2.12 to 3.36 million fish (Fig. 5), median percent infected ranged from 33% to 58% per year (Fig. 6), and median percent disease deaths ranged from 11% to 30% per year (Fig. 7). With vaccination, mean abundance increased by 32% to 356%, with the largest increase occurring under the high clustering level (Table 2, Fig. 5). Median percent infected and median percent disease deaths decreased by 62% and 51% per year, respectively (Table 2, Figs. 6, 7), under the high clustering level. For the other clustering levels, median percent infected decreased by 25% to 42% per year (Table 2, Fig. 6), whereas median percent disease deaths decreased by 8% to 21% per year (Table 2, Fig. 7).

For the high infection probability and low exposure mortality scenarios, simulation-averaged abundance in the absence of vaccination ranged from 4.56 to 4.68 million depending on the assumed clustering level (Fig. 5). Median percent

Table 2. Relative difference in abundance and absolute difference in percent mortality and percent infected over the last 10 yr of the individual-based model simulations for all scenarios.

Infection probability	Mortality probability	Cluster	Relative difference in abundance (%)	Actual difference in percent infected (%)	Actual difference in percent deaths due to disease (%)
High	High	High	208.14	-58.50	-41.58
High	High	Med	167.36	-54.63	-35.47
High	High	Low	133.06	-51.60	-30.73
High	High	ExtraLow	54.52	-39.02	-15.99
High	Low	High	3.95	-34.42	-1.55
High	Low	Med	1.50	-33.74	-1.14
High	Low	Low	1.72	-33.23	-0.98
High	Low	ExtraLow	1.25	-28.91	-0.50
Low	High	High	355.71	-61.78	-51.40
Low	High	Med	78.26	-42.03	-21.29
Low	High	Low	53.22	-36.35	-15.47
Low	High	ExtraLow	31.80	-25.20	-8.29
Low	Low	High	6.80	-33.78	-2.02
Low	Low	Med	0.69	-29.95	-0.75
Low	Low	Low	2.17	-27.23	-0.49
Low	Low	ExtraLow	-0.81	-22.57	-0.24

Notes: Relative differences in abundance [(Abundance with vaccination - Abundance without vaccination)/Abundance with without vaccination]. Absolute differences in percent mortality and percent infected due to vaccination were calculated as [% mortality with vaccination - % mortality without vaccination].

infected in the absence of vaccination ranged from 46% to 55% per year, which was slightly lower than the median percent infected in the absence of vaccination for the high infection probability and high exposure mortality scenario (Fig. 6). Median percent disease deaths ranged from 1% to 2% per year regardless of the clustering levels (Fig. 7). With vaccination, abundance increased by 1% to 4% relative to the abundance levels without vaccination depending on the assumed clustering level (Table 2). Simulation-averaged abundance ranged from 4.69 and 4.74 million fish, which was just slightly lower than mean abundance from the calibration scenario (Fig. 5). With vaccination, median percent infected declined by 29% to 34% per year (Table 2, Fig. 6), whereas median percent disease deaths declined by <2% per year regardless of the clustering level (Table 2, Fig. 7).

For the low infection and low exposure mortality scenarios, depending on the assumed clustering level, mean abundance ranged from 4.46 to 4.79 million fish without vaccination and 4.71 and 4.80 million fish with vaccination (Fig. 5), suggesting the benefits from vaccination were small. Simulation-averaged median percent infected ranged from 31% to 53% without vaccination and 8% to 20% with vaccination, with the highest annual percent infected occurring under the high clustering scenario (Fig. 6). The highest percent disease deaths among this group of scenarios was 3% per year under the high clustering scenario in the absence of vaccination (Fig. 7). For all other examined scenarios, median percent disease deaths ranged from 0.4% to 1.2% per year without vaccination (Fig. 7). With vaccination, median percent disease deaths decreased by 0.2% to 2.0% depending on the clustering assumption (Table 2).

Sensitivity simulations

Doubling the stocking level to 4.8 million fish approximately doubled the abundance level of Chinook salmon across the range of modeled scenarios, but had essentially had no effect on percent infected or disease deaths (Table 3) meaning there was no additional protective effect stemming from the higher stocking rate. Changing the population initialization status to 90% susceptible individuals, 5% shedding individuals, and 5% recovered individuals had no effect on any of the performance metrics (Table 3).

When recovered individuals were no longer able to resume shedding of virus particles, the disease was eradicated (i.e., percent infected and disease deaths equaled 0%) from the system regardless of whether or not stocked individuals were vaccinated for the highest clustering level (Table 3). This was observed for both mortality scenarios. Under the low and medium clustering levels, disease was still present in the system in the absence of vaccination. However, with vaccination, the disease was eradicated from the system under the low and medium clustering levels (Table 3). Under the lowest assumed clustering level, vaccination decreased both the median percent infected (20–25%) and percent disease deaths (1–22%) depending on the mortality level, which was comparable to the reduction observed under the baseline simulations.

DISCUSSION

Disease outbreaks are believed to be an important regulatory component of some fish populations (Fenichel et al. 2009, Marty et al. 2010, Lafferty et al. 2015). As such, it is important to understand both disease dynamics and potential management actions that can combat disease spread and promote sustainable and healthy fish populations. The importance of understanding how management actions such as stocking vaccinated fish can combat disease spread perhaps cannot be overstated given that an anticipated consequence of climate change is an elevated risk of disease in aquatic environments due to thermal stress and expansion/elevated growth of pathogens (Harvell et al. 2002). Previous modeling studies of disease dynamics have pointed to the importance of fish stocking and biosecurity measures in hatchery systems to disease persistence in fish populations (Fenichel et al. 2009, Turner et al. 2014), but to our knowledge this is the first study to evaluate the potential of vaccinating hatchery-propagated fish as a means to confer protection to a wild fish population against disease spread.

Through our modeling, we demonstrated that a protective effect could be elicited in a large fish population through a program designed around the vaccination and release of hatchery-propagated individuals, at least under certain conditions. The extent of protection stemming from this type of vaccination program depended on

Table 3. Simulation-averaged abundance (millions of fish), percent infected (infections; %), and percent disease deaths (mortality; %) for baseline simulations (2.4 M) and sensitivity scenarios (4.8 M = 4.8 million stocking level; NR = recovered individuals could not resume shedding; AI = alternative population initialization status) by mortality probability (Mort. prob.), clustering level (Cluster.), and whether stocked individuals were vaccinated (Vac.).

Mort. prob.	Cluster.	Vac.	Variable	2.4 M	4.8 M	NR	AI
High	High	No	Abundance	1.15	2.31	4.90	1.16
High	High	Yes	Abundance	3.54	7.14	4.90	3.55
High	Med	No	Abundance	1.33	2.73	2.94	1.33
High	Med	Yes	Abundance	3.55	7.10	4.85	3.54
High	Low	No	Abundance	1.54	3.13	1.28	1.53
High	Low	Yes	Abundance	3.58	7.20	4.80	3.58
High	ExtraLow	No	Abundance	2.46	4.88	2.21	2.45
High	ExtraLow	Yes	Abundance	3.80	7.71	3.95	3.88
Low	High	No	Abundance	4.56	9.02	7.10	4.53
Low	High	Yes	Abundance	4.74	9.42	9.43	4.75
Low	Med	No	Abundance	4.63	9.27	9.42	4.55
Low	Med	Yes	Abundance	4.70	9.50	9.23	4.77
Low	Low	No	Abundance	4.62	9.23	9.54	4.60
Low	Low	Yes	Abundance	4.69	9.57	9.02	4.75
Low	ExtraLow	No	Abundance	4.68	9.43	7.20	4.75
Low	ExtraLow	Yes	Abundance	4.74	9.54	2.73	4.85
High	High	No	Infections	76.40	76.34	0.00	76.30
High	High	Yes	Infections	17.90	18.28	0.00	17.96
High	Med	No	Infections	72.64	72.53	32.50	72.56
High	Med	Yes	Infections	18.01	17.58	0.00	17.56
High	Low	No	Infections	68.67	68.61	60.13	68.73
High	Low	Yes	Infections	17.07	17.53	0.00	17.05
High	ExtraLow	No	Infections	54.44	54.89	32.22	54.52
High	ExtraLow	Yes	Infections	15.42	15.80	6.98	16.09
Low	High	No	Infections	54.51	54.27	0.00	54.39
Low	High	Yes	Infections	20.08	20.01	0.00	20.06
Low	Med	No	Infections	53.27	53.28	10.90	53.27
Low	Med	Yes	Infections	19.53	20.13	0.00	19.99
Low	Low	No	Infections	52.03	52.07	42.33	52.33
Low	Low	Yes	Infections	18.80	19.25	0.00	19.45
Low	ExtraLow	No	Infections	45.84	46.04	29.76	45.66
Low	ExtraLow	Yes	Infections	16.93	16.96	9.27	17.57
High	High	No	Mortality	52.48	52.70	0.00	52.18
High	High	Yes	Mortality	10.91	11.01	0.00	10.98
High	Med	No	Mortality	46.69	46.04	28.22	46.58
High	Med	Yes	Mortality	11.22	10.77	0.00	10.89
High	Low	No	Mortality	41.03	40.57	52.04	41.07
High	Low	Yes	Mortality	10.30	10.42	0.00	10.22
High	ExtraLow	No	Mortality	23.90	24.34	27.74	24.09
High	ExtraLow	Yes	Mortality	7.91	7.92	5.90	8.13
Low	High	No	Mortality	2.22	2.22	0.00	2.20
Low	High	Yes	Mortality	0.67	0.67	0.00	0.69
Low	Med	No	Mortality	1.78	1.77	0.56	1.78
Low	Med	Yes	Mortality	0.64	0.67	0.00	0.66
Low	Low	No	Mortality	1.57	1.56	2.13	1.58
Low	Low	Yes	Mortality	0.58	0.60	0.00	0.61
Low	ExtraLow	No	Mortality	0.90	0.90	1.47	0.89
Low	ExtraLow	Yes	Mortality	0.40	0.40	0.45	0.41

Note: Sensitivity scenarios were conducted for the high infection probability level only.

factors such as infection probability, exposure mortality, assumptions regarding fish clustering, and whether recovered individuals could periodically renew shedding of virus particles. When recovered SIs could renew shedding of virus particles, decreases in percent infected from vaccination ranged from 40% to nearly 60% under conditions of high infection probability and high exposure mortality regardless of clustering and stocking level. An even larger decrease in percent infected (74% decrease in infections) resulted from vaccination under a condition of low infection probability, high exposure mortality, and high clustering. For most other conditions examined, vaccination decreased percent infected by anywhere from 23% to around 40% when recovered individuals could begin renewed shedding of viral particles. Vaccination similarly resulted in the largest relative increases in abundance under conditions of high infection probability and high exposure mortality regardless of clustering assumptions and under a condition of low infection probability, high exposure mortality, and high clustering.

Our finding that the annual percent infected and the effectiveness of vaccination was greatest under conditions of low infection, high mortality, and high clustering was somewhat unexpected given that the low infection probability corresponded to an infection probability of 10%, whereas the high infection probability corresponded to an infection probability of 65%. We attribute this result to differences in duration of population infectiousness under the different scenarios (Reno 1998). Under the high infection and high clustering scenario, disease outbreaks were highly acute, and thus, the period of infectiousness was relatively brief. Conversely, under the low infection probability scenario, period of infectiousness was longer, and therefore, there was more opportunity to expose susceptible individuals to the disease (Reno 1998). While unusual for VHS-like (viral hemorrhagic septicemia) diseases, high exposure mortality and low infection dynamics for pathogens can occur (e.g., chronic wasting disease, Foley et al. 2016). This suggests that from a population perspective there can be benefits to a disease emerging rapidly and infecting a high proportion of the population very quickly rather than a disease emerging more slowly over the course of the year at least in cases

where probability of death of infected individuals is based on virus exposure level.

While the release of vaccinated hatchery-propagated fish lowered percent infected and increased population abundance, only in scenarios where recovered individuals could not resume shedding of virus particles did we observe cases where percent infected dropped to 0% by the end of the modeled time period. In some cases, infection dropped to 0% even in the absence of vaccinating hatchery fish when recovered individuals could not resume shedding. This constitutes a fading out of the virus given that all simulation models, with the exception of one sensitivity scenario, were initialized under an assumption that 50% of the population were infected or susceptible to infection. We draw two main conclusions from this modeling result. First, it suggests that renewed shedding of virus particles by recovered individuals can be a significant factor affecting persistence of diseases in endemic waterbodies. Similarly, Kramer-Schadt et al. (2009) using a spatially explicit IBM showed that persistence of classical swine fever in wild boars was most likely to occur when infected individuals recovered but continued to infect newly susceptible individuals over long time periods. In the case of VHSV-IVb, Kim and Faisal (2012) theorized that renewed shedding by recovered individuals during periods of a stress could be a mechanism by which VHSV-IVb is maintained in endemic waterbodies, and our modeling results support this theory.

The second conclusion that we can draw from our results is that to elicit a full herd immunity response in a population such as Lake Michigan Chinook salmon against a virus exhibiting characteristics similar to what was considered herein would likely necessitate a major increase in stocking levels. The highest stocking rate considered in our research was 4.8 million fish, which, as previously indicated, was the average stocking level of Chinook salmon in Lake Michigan from 1990 to 2014. Thus, our model suggests that, without drastically increasing stocking, disease eradication is unlikely so long as recovered individuals can continue being intermittent sources of new infections.

Our finding that the higher stocking level of vaccinated individuals did not result in any additional protective effect to the at-large population

may have resulted from the higher stocking level elevating the densities of susceptible individuals via their offspring, which facilitated maintenance of the disease despite the greater number of vaccinated individuals being released into the system. Population density is one of the main factors influencing disease dynamics in infected systems (Reno 1998). For this reason, culling of populations to reduce densities is one way to combat disease spread (Reno 1998, Lafferty et al. 2015). A traditional vaccination program designed around the vaccination of individuals from the at-large population also can result in greater densities of susceptible individuals via offspring produced from vaccinated individuals to some extent; however, the scale of this issue would arguably be far greater and potentially more problematic in vaccination programs designed around hatchery releases of fish. When relying on such a vaccination program, the most effective release program perhaps would be to stock at extremely high levels for brief periods of time (e.g., one or two years) to disrupt the transmission of disease prior to the vaccinated individuals maturing and having an opportunity to reproduce and add to the pool of susceptible individuals.

Various assumptions were made with the IBM used for this research, and it is important to consider how some of these assumptions affected our results. First, we assumed that infection could occur at any time of the year. Thus, susceptible individuals were at risk of infection throughout their entire lives. If we had instead limited disease spread to only occurring during particular time periods, such as during spawning periods or others points of stress, infections likely would have decreased and the protective effect offered from vaccinating and releasing hatchery-propagated individuals may have increased. We also assumed that vaccination afforded 100% protection against disease throughout a fish's entire life span. If we had instead assumed a lesser level of protection or assumed that the level of protection decreased over time, the degree of protection afforded to the at-large Chinook salmon population would have declined. We also assumed that the only method of infection for Chinook salmon was to reside in the same vicinity as at least one other infected individual. In reality, Chinook salmon would be just one component of an aquatic community comprised of other species with

differing levels of vulnerability to the disease. It is therefore possible for fish to become infected through contact with other species or via consumption of infected individuals. Another potential avenue for infection is via vertical transmission from broodstock to offspring, which has been shown to be important in other fish diseases (e.g., bacterial kidney disease; Fenichel et al. 2009) and can make it easier for diseases to persist in populations (Reno 1998). We ultimately chose to model Chinook salmon in isolation because of the computational aspects associated with modeling a larger fish community. Additionally, it is not uncommon in modeling studies such as this to consider a single species in isolation even though disease transmission can involve other species (Eisinger and Thulke 2008, Fenichel et al. 2009, Rees et al. 2013). Similar to the above, we did not consider competition or condition aspects in our model. Competition for food and condition would have made for more realistic model results, but we did not have the data by which to populate the model for these factors and suggest that future modeling efforts would benefit greatly from information on how condition impacts foraging success and infection and mortality probabilities. An additional assumption that was implicit to our model was that stocked individuals behaved similarly to wild-produced fish with respect to dispersal and experienced the same dynamics apart from those related to disease. If instead, dispersal or dynamics of stocked fish differed from that of the at-large population, the protective effect of the vaccination program would likely be reduced.

One of the more difficult aspects of our modeling effort was how to model disease transmission. We used VHSV-IVb as the basis for many disease aspects of our model; however, experiments that have been conducted on VHSV-IVb have generally involved infecting individuals either directly through injection (Kim and Faisal 2010*a, b, c*) or immersion in small tanks (Kim and Faisal 2010*c*, Weeks et al. 2011, Millard and Faisal 2012, Standish et al. 2016*b*). However, none of these experimental exposure routes were conducive to modeling when the scale of the model was Lake Michigan. Even though a 1.8-km² grid may seem like a coarse approximation to Lake Michigan, the spatial database consisted of more than 14 thousand cells. A finer spatial resolution would have

been difficult to implement from a computational standpoint. Our approach of grouping individuals located within a grid cell as a means of modeling exposure was the most straightforward approach for trying to scale laboratory studies to a real-world application. At the finest scale, we grouped fish into 100 groups and allowed group structure to change daily. This undoubtedly affected the result of the model, and we recommend further study into how to spatially represent fish for disease modeling purposes given that space has been shown to be important in disease dynamics (Eisinger and Thulke 2008, Lange et al. 2012).

In conclusion, our model suggests that, under various assumptions of infection probability, exposure mortality, and clustering, vaccinated hatchery fish can significantly reduce infections in at-large fish populations, but eliminating the disease from a population may not be feasible, particularly when recovered individuals may still infect susceptible individuals. Vaccinating hatchery fish may be a mechanism to minimize disease spread in at-risk populations when disease is persistent and mortality is high. We recommend further model-based evaluations of factors that can influence the efficacy of vaccination programs designed around the vaccination and release of hatchery-propagated individuals in protecting wild fish populations against disease outbreaks; we believe it is likely that interest in using this type of vaccination programs to protect wild fish populations is likely to increase in the future. In particular, we believe it would be beneficial to explore how efficacy of vaccination programs can be affected when behavior and dynamics of stocked individuals differ from that of wild conspecifics and how imperfect protection can influence the protective effect from vaccination program.

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