

Supplementary materials for

Influenza vaccine allocation in tropical settings under constrained resources

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S1. Model specification

Few models exist that attempt to fit three co-circulating (sub)types of influenza in a tropical region [1], so we adapted our previous model fit for a single nonannual pathogen [2] to fit multiple types and subtypes of influenza. A model diagram can be found in Figure S1. In our adapted model, each (sub)type follows SIRS dynamics with a two-stage infected class and a four-stage recovered class to allow duration of infection and duration of infection-induced immunity to be Erlang distributed [3].

In addition to baseline transmission parameters for each (sub)type (denoted $\beta_{\tilde{s}}$ in the equations below, where $\tilde{s}$ refers to any particular (sub)type), we included temporary periods of increased transmission for epidemics. The timings of these transmission peaks (denoted φ_k) are a linear combination of parameters representing the time intervals between periods of increased transmission (denoted τ_k), which were estimated from a previously fit normal distribution of epidemic timings from ten years of sentinel surveillance from fifteen hospitals located throughout Vietnam [2]. The period of increased transmission lasts for a duration of time denoted δ , with a magnitude of increased transmission denoted a .

The total duration of infection, denoted ν , was assumed to be five days. Hospitalization can occur following the first infectious state, using a hospitalized fraction (denoted h) based on data from the US Centers for Disease Control and Prevention (CDC) [4]. Death occurs from the hospital at a rate (denoted d) based on CDC data [4]; we assumed that deaths only occur after hospitalization. Infection with one (sub)type confers full immunity from that (sub)type and partial immunity to the others, using quantities of partial immunity (denoted σ_{ij}) estimated previously in published literature [1]. The duration of immunity is denoted ρ^{-1} .

Single cases are sporadically introduced into the population at fixed intervals to represent case importation. Single cases are, at these intervals, moved from the Susceptible compartment into an Infected compartment, alternating across (sub)types and age groups.

We incorporated age structure into the model by dividing the population into decade-based age groups, with the last group consisting of adults 70 years and older, using published age demographics in Vietnam [5]. We incorporated a crude birth rate as reported by the World Bank [6] and an age-based natural death rate as reported by the World Health Organization [7]. Risk of hospitalization and death vary by age group based on reported hospitalization and death fractions reported by the CDC [4]. Age-based contact mixing was incorporated into the model (denoted by η_{ij} in the equations below) by using previously estimated age-based contact patterns for Vietnam [8,9].

We introduced vaccination into the model by creating a set of compartments for vaccinated individuals. In order to account for vaccines not only preventing infection but also reducing risk of severe outcomes (hospitalization or death) following infection, this included a set of infected, hospitalized, and recovered classes among those vaccinated (Figure S1). Based on previous research regarding vaccine protection against infection [10], hospitalization [11–13], and death [14], we assumed a 50% effectiveness in preventing infection, 50% effectiveness in preventing hospitalization from infection, and 50% effectiveness in preventing death from hospitalization (denoted ξ). We also assumed an exponentially distributed duration of vaccine-induced immunity (denoted ρ_v^{-1}), with a mean duration of 270 days. Under this assumption, approximately half of vaccinated individuals retain protection after six months, and approximately a quarter retain protection after one year, which is broadly consistent with previous findings [15].

The model is specified by the following equations, with parameters used shown in Table S1:

$$\begin{aligned}
\frac{dS_{\tilde{a}}}{dt} &= - \sum_a \sum_s \eta_{a\tilde{a}} \beta_s(t) S_{\tilde{a}} (I_{as}^1 + I_{as}^2 + vI_{as}^1 + vI_{as}^2) + \sum_s \frac{\rho}{4} R_{\tilde{a}s}^4 + \sum_s \frac{\rho}{4} vR_{\tilde{a}s}^4 + \rho_v V_{\tilde{a}} \\
\frac{dI_{\tilde{a}\tilde{s}}^1}{dt} &= \sum_a \eta_{a\tilde{a}} \beta_{\tilde{s}}(t) S_{\tilde{a}} (I_{a\tilde{s}}^1 + I_{a\tilde{s}}^2 + vI_{a\tilde{s}}^1 + vI_{a\tilde{s}}^2) \\
&\quad + \sum_a \sum_{s \neq \tilde{s}} \sum_{i=1}^4 \eta_{\tilde{a}a} \beta_{\tilde{s}}(t) \sigma_{\tilde{s}s} R_{\tilde{a}s}^i (I_{a\tilde{s}}^1 + I_{a\tilde{s}}^2 + vI_{a\tilde{s}}^1 + vI_{a\tilde{s}}^2) - \frac{h_{\tilde{a}} v}{2} I_{\tilde{a}\tilde{s}}^1 \\
&\quad - \frac{(1 - h_{\tilde{a}}) v}{2} I_{\tilde{a}\tilde{s}}^1 \\
\frac{dI_{\tilde{a}\tilde{s}}^2}{dt} &= \frac{(1 - h_{\tilde{a}}) v}{2} I_{\tilde{a}\tilde{s}}^1 - \frac{v}{2} I_{\tilde{a}\tilde{s}}^2 \\
\frac{dH_{\tilde{a}\tilde{s}}}{dt} &= \frac{h_{\tilde{a}} v}{2} I_{\tilde{a}\tilde{s}}^1 - \frac{d_{\tilde{a}} v}{2} H_{\tilde{a}\tilde{s}} - \frac{(1 - d_{\tilde{a}}) v}{2} H_{\tilde{a}\tilde{s}} \\
\frac{dR_{\tilde{a}\tilde{s}}^1}{dt} &= \frac{v}{2} I_{\tilde{a}\tilde{s}}^2 + \frac{(1 - d_{\tilde{a}}) v}{2} H_{\tilde{a}\tilde{s}} - \frac{\rho}{4} R_{\tilde{a}\tilde{s}}^1 - \sum_a \sum_{s \neq \tilde{s}} \eta_{a\tilde{a}} \beta_s(t) \sigma_{\tilde{s}s} R_{\tilde{a}\tilde{s}}^1 (I_{as}^1 + I_{as}^2 + vI_{as}^1 + vI_{as}^2) \\
\frac{dR_{\tilde{a}\tilde{s}}^i}{dt} &= \frac{\rho}{4} R_{\tilde{a}\tilde{s}}^{i-1} - \frac{\rho}{4} R_{\tilde{a}\tilde{s}}^i - \sum_a \sum_{s \neq \tilde{s}} \eta_{a\tilde{a}} \beta_s(t) \sigma_{\tilde{s}s} R_{\tilde{a}\tilde{s}}^i (I_{as}^1 + I_{as}^2 + vI_{as}^1 + vI_{as}^2), i \in \{2, 3, 4\} \\
\frac{dV_{\tilde{a}}}{dt} &= - \sum_a \sum_s \eta_{a\tilde{a}} \xi \beta_s(t) V_{\tilde{a}} (I_{as}^1 + I_{as}^2 + vI_{as}^1 + vI_{as}^2) - \rho_v V_{\tilde{a}} \\
\frac{dvI_{\tilde{a}\tilde{s}}^1}{dt} &= \sum_a \eta_{a\tilde{a}} \xi \beta_{\tilde{s}}(t) V_{\tilde{a}} (I_{a\tilde{s}}^1 + I_{a\tilde{s}}^2 + vI_{a\tilde{s}}^1 + vI_{a\tilde{s}}^2) \\
&\quad + \sum_a \sum_{s \neq \tilde{s}} \sum_{i=1}^4 \eta_{\tilde{a}a} \xi \beta_{\tilde{s}}(t) \sigma_{\tilde{s}s} vR_{\tilde{a}s}^i (I_{a\tilde{s}}^1 + I_{a\tilde{s}}^2 + vI_{a\tilde{s}}^1 + vI_{a\tilde{s}}^2) - \frac{\xi h_{\tilde{a}} v}{2} vI_{\tilde{a}\tilde{s}}^1 \\
&\quad - \frac{(1 - \xi h_{\tilde{a}}) v}{2} vI_{\tilde{a}\tilde{s}}^1 \\
\frac{dvI_{\tilde{a}\tilde{s}}^2}{dt} &= \frac{(1 - \xi h_{\tilde{a}}) v}{2} vI_{\tilde{a}\tilde{s}}^1 - \frac{v}{2} vI_{\tilde{a}\tilde{s}}^2 \\
\frac{dvH_{\tilde{a}\tilde{s}}}{dt} &= \frac{\xi h_{\tilde{a}} v}{2} vI_{\tilde{a}\tilde{s}}^1 - \frac{\xi d_{\tilde{a}} v}{2} vH_{\tilde{a}\tilde{s}} - \frac{(1 - \xi d_{\tilde{a}}) v}{2} vH_{\tilde{a}\tilde{s}}
\end{aligned}$$

$$\begin{aligned}
\frac{dvR_{\tilde{a}\tilde{s}}^1}{dt} &= \frac{\nu}{2}vI_{\tilde{a}\tilde{s}}^2 + \frac{(1-\xi d_{\tilde{a}})\nu}{2}vH_{\tilde{a}\tilde{s}} - \frac{\rho}{4}vR_{\tilde{a}\tilde{s}}^1 \\
&\quad - \sum_a \sum_{s \neq \tilde{s}} \eta_{a\tilde{a}} \xi \beta_s(t) \sigma_{\tilde{s}s} vR_{\tilde{a}\tilde{s}}^1 (I_{as}^1 + I_{as}^2 + vI_{as}^1 + vI_{as}^2) \\
\frac{dvR_{\tilde{a}\tilde{s}}^i}{dt} &= \frac{\rho}{4}vR_{\tilde{a}\tilde{s}}^{i-1} - \frac{\rho}{4}vR_{\tilde{a}\tilde{s}}^i - \sum_a \sum_{s \neq \tilde{s}} \eta_{a\tilde{a}} \xi \beta_s(t) \sigma_{\tilde{s}s} vR_{\tilde{a}\tilde{s}}^i (I_{as}^1 + I_{as}^2 + vI_{as}^1 + vI_{as}^2), i \in \{2, 3, 4\} \\
\beta_{\tilde{s}}(t) &= \begin{cases} \beta_{0\tilde{s}} \left[1 + a_{\tilde{s}} \cos^+ \left(\frac{2\pi(\varphi_{k\tilde{s}} - t)}{2\delta_{\tilde{s}}} \right) \right], & \varphi_{k\tilde{s}} - \frac{\delta_{\tilde{s}}}{2} \leq t \leq \varphi_{k\tilde{s}} + \frac{\delta_{\tilde{s}}}{2} \\ \beta_{0\tilde{s}}, & \text{otherwise} \end{cases} \\
\varphi_{k+1,\tilde{s}} &= \varphi_{k\tilde{s}} + \tau_{k\tilde{s}}
\end{aligned}$$

where $\tilde{a}$ denotes any particular age group and $\tilde{s}$ denotes any particular (sub)type of influenza.

Expanding our model from one pathogen to three does not guarantee that all three influenza (sub)types co-circulate with asynchronous epidemic behavior (i.e. without reaching an endemic state). Influenza dynamics in Vietnam have showed subtypes A/H1, A/H3, and type B experience epidemic peaks of varying sizes that occur asynchronously (with B epidemics showing periods of flat incidence approximately half of the time) [2,16]. Therefore, we aimed to adapt our model to emulate asynchronous behavior to better reflect influenza dynamics in Vietnam. In doing so, we used the known annual attack rate [17] and previously inferred variances in timing of epidemic peaks [2] to identify this model behavior. Because neither strong annual nor nonannual cycles were detected in Vietnam previously, we did not fit the model to the observed data since it is unrealistic to assume that the observed trends over ten years will be prescriptive or representative of future dynamics.

We used known epidemiological quantities in Vietnam (annual attack rate and variance in timings between epidemic peaks) and elsewhere (hospitalization fraction and mortality fraction) to inform model parameterization. To account for the uncertainty in model parameters and to avoid producing results that are sensitive to assumed parameter values

[18], we considered multiple parameterizations. We assumed a five-day duration of infection, and cross-immunity among subtypes based on previous literature [1]. We assumed vaccine effectiveness and duration based on previous literature [10–15]. For remaining model parameters (baseline transmission for each (sub)type $\beta_{0H1}, \beta_{0H3}, \beta_{0B}$; duration of infection-induced immunity ρ^{-1} ; magnitude a , timing τ_k , and duration δ of epidemic peaks for each (sub)type; and frequency of sporadic case introduction), we conducted a random parameter search to identify parameter combinations that are epidemiologically consistent with influenza dynamics in Vietnam. The parameter search is in the form of an Approximate Bayesian Computation where a set of seven conditions must be satisfied for acceptance. We ran the model for a 20-year burn-in period, followed by a 10-year period where we compared model output to expected dynamics seen in Vietnam to identify realistic parameter sets. We classified parameter combinations as epidemiologically consistent with influenza dynamics observed in Vietnam if they produce stable forward dynamics with asynchronous co-circulation of the three (sub)types without settling into endemic equilibrium. In order to identify parameter sets meeting these conditions, we set seven criteria that must all be met. The seven criteria are based on observed data and/or literature, either directly or through qualitative observations of similarity to the observed data. The seven criteria are as follows:

- i) Standard deviation of daily incidence values for each (sub)type are greater than 100 (in a population of one million). This was to avoid model parameterizations that led to static equilibrium or near-constant values, including virus extinction.
- ii) Pairwise correlations between pairs of (sub)types are less than 0.7 in absolute value. This was to assure that they peak/trough times for each (sub)type did not consistently align, as they infrequently aligned in the observed data.
- iii) Among the maximum daily incidence values of each (sub)type, the lowest maximum value is no less than 70% of the highest maximum incidence value. This was to prevent one (sub)type from having substantially higher incidence/peaks compared to the others, which was not seen in the observed data. This also assured that no (sub)types went extinct.

- iv) The three maximum daily incidence values must span at least one year (i.e. all three peaks cannot be in the same 365-day period). This avoided situations where one single year had an unrealistically high share of the incidence over our ten-year observation period.
- v) Within each (sub)type, between 25 and 75% of daily incidence values are less than 100 (in a population of one million). This was to assure that each (sub)type had adequate periods of low incidence to obtain discrete epidemics, which were seen in the observed data. This avoided model outputs where incidence varied, but with higher average/minimum values than are seen in the observed data.
- vi) All-influenza annual attack rates (combining all (sub)types) are between 10 and 40%. This was based on previous literature [17].
- vii) All-influenza annual attack rates are not monotonically increasing or decreasing over time. This was to assure our model did not show trends towards an equilibrium value or extinction to better reflect the observed data.

Model parameters are listed in Table S1, including distributions from which we drew parameter values in the parameter search. We chose the first 50 parameter sets that satisfied all seven criteria described previously to assure our results are robust to realistic parameterizations. Distributions of the parameter values are presented in Figure 1, and annual attack rates in the simulation are shown in Figure S2. Among the 10 years in the simulation and 50 parameter combinations ($n = 500$), greater density is seen among the lower values of the allowed range in attack rate. This likely occurs because years with higher attack rates ($> 30\%$) are typically followed by years of lower attack rates. The attack rates in years following those in which the attack rate was greater than 30% have lower median and IQR values compared to the set of all attack rates as well as the subset of attack rates less than 30% (Figure S2).

S2. Assigning vaccine allocations

In order to identify vaccine allocations that best reduce mortality, we examined a large number of allocations for each vaccine supply to see which allocation led to lowest average annual mortality. Each of these allocations consists of a set of eight numbers corresponding to the proportion of vaccines allocated to each age group, which can be algebraically translated into vaccine coverage proportions for each age group. Each set of eight numbers was randomly drawn to represent a wide variety of ways to distribute vaccines to eight different age groups. In order to assure that high vaccine coverage was considered for all age groups for each vaccine supply, we used a three-step process for each vaccine supply:

1. Draw Latin hypercube samples representing the percentage of each age group that is covered in vaccination (sets of eight numbers ranging between zero and one). Keep only those that yield vaccine totals above the specified amount but less than the specified amount plus two percentage points. Scale all eight values down to achieve the exact vaccine supply.
2. For each age group, repeat step 1 with the additional constraint of keeping only samples where coverage in that age group exceeds 95% (or 95% of the maximum possible coverage for the 10% vaccine supply). Repeat until each age group contains a minimum of 25 samples with high coverage.
3. Repeat step 1 until the desired total number of allocations is achieved.

We drew 10,000 total samples for supply levels ranging between 10 percent and 60 percent of the population. At higher supply levels, there are fewer possible feasible allocations, so fewer sampled allocations were needed to achieve a full range of possible coverage values. We drew 7,500 samples for the 70 percent supply, 5,000 samples for the 80 percent supply, and 2,000 samples for the 90 percent supply. We applied each allocation to the 50 parameter sets and averaged their average annual mortality to evaluate the effectiveness of each allocation in reducing mortality.

S3. Sensitivity analyses

We assumed a vaccine effectiveness of 50% against infection, against hospitalization if infected, and against death if hospitalized. While this is consistent with previous estimates for vaccine effectiveness in reducing infection and death, we examined different vaccine effectiveness values since it has been observed to change across years. To see if optimal strategies differ, we repeated our analyses using 30, 40, 50, 60, and 70% vaccine effectiveness. Under a vaccine effectiveness of 30% or 40%, targeting elderly adults generally led to lowest annual mortality, particularly when vaccine supplies were lower. As vaccine effectiveness increased to 50% or greater, the allocations leading to lowest mortality favored vaccinating younger age groups (Figure S5, S6). The magnitude of differences in vaccine allocations can be large; when examining the ten allocations with lowest mortality under a 10% supply, we see very few vaccines are allocated to the 10-19 group under 30% effectiveness, a mix of allocations with very low and very high doses allocated to the 10-19 group under 40% effectiveness, and nearly all vaccines allocated to the 10-19 group when effectiveness is 50% or higher (Figure S5).

Figure S6 shows the share of each age group that comprises the 10 allocations leading to lowest mortality across vaccine supplies and vaccine effectiveness values by averaging the percentage of doses allocated to each age group among the ten. Within each vaccine supply, increases in the share of doses allocated to younger age groups generally increases as vaccine effectiveness increases. This change is most substantial when vaccine supplies are lower since most effective allocations more closely resemble population demographics when vaccine supplies are high.

Estimates regarding vaccine immunity waning are also uncertain. Previous studies have produced varying estimates for the duration of immunity following vaccination. Therefore, in addition to a nine-month average immune duration, we repeated our analyses with mean immune durations between six and twelve months. As mean duration of vaccine-induced immunity decreases toward six months, the vaccination allocations minimizing mortality increasingly overrepresented elderly adults, particularly with lowest vaccine supply (10-

20%). Increasing mean duration toward 12 months, more allocations overrepresenting school-age children (10-19) and working adults (20-39) minimized mortality (Figure S7). Particularly in the 10% supply, the allocations leading to minimum mortality largely do not include the 10-19 age group when the duration is seven months or less, but then primarily include this age group when the duration is ten months or higher. Under 8 to 11-month average duration, the optimal allocation under a 10% supply allocates nearly all vaccines to the 10-19 age group, but under a 12-month duration, allocating vaccines to other groups as well is optimal (though the 10-19 group still receives a majority of vaccines). The magnitude of change is shown in Figure S8, where the share that each age group comprises among the ten allocations with lowest mortality changes under assumed vaccine immunity durations. Across vaccine supplies, increasing the duration of immunity leads to the 60-69 and 70+ age groups comprising a lower share of vaccination in the most effective allocations, while the 0-9 and 10-19 groups comprise a larger share.

Vietnam has a younger population structure compared to countries in North America and Europe, with the 2019 median age in Vietnam being 31, while median ages of countries in North America and Europe range between 37 and 46 [19]. In order to see if our results favoring vaccinating younger age groups over older age groups would change if elderly adults comprised a larger share of the population, we examined different population structures. Using the United States and Vietnam as benchmarks, we repeated our analyses with populations having age structures of Vietnam, the United States, and three intermediate populations consisting of mixture distributions with weights of .25, .50, and .75 for each country. Estimated mortality and mortality-minimizing vaccine allocations change little under different population distributions (Figures S9, S10). Under lower vaccine supplies, among the ten allocations that minimize mortality, the average share of doses allocated to different age groups remains constant (Figure S10). Under higher vaccine supplies, more changes are seen: in a population with age demographics resembling the US, the set of ten mortality-minimizing vaccine allocations allocate a higher share to the oldest age groups compared to a population with age demographics resembling Vietnam. This is likely reflective of the change in age demographics, as

previously, the best vaccine allocations under higher vaccine supplies more closely resemble the population demographics compared to under lower supplies (Figures 3, 4).

Our analyses assumed that social contact does not change over time. Few previous studies exist that examine, under ordinary circumstances, how social mixing patterns change throughout the course of a year. However, it is likely that social contact patterns change as a result of social factors such as school years, holidays, or reactions to climatic conditions such as temperature. In order to determine whether our results are sensitive to the assumption of a constant contact matrix, we repeated our analyses using different changes to contact mixing. The first considers the effect of school years, where the three months outside of the academic year (June, July, and August) have reduced social contact in the two youngest age groups (0-9 and 10-19). The second considers the effect of climatic factors, where social contact decreases through the summer months, following a U-shaped pattern over the course of 6 months (May through October) resembling results seen previously in Shanghai [20]. For both analyses, we considered decreases in social mixing of 25%, 50%, and 75%. The third change to contact mixing considers increases in contact mixing during the Lunar New Year Holiday, which we simulated by increasing social mixing in all age groups during the month of February. Similarly, the magnitudes of considered increases were 25%, 50%, and 75%. Within these analyses, introducing an annual component to a parameter directly related to transmission led to greater advantages being seen when targeting a specific time of year for vaccination. When reducing contact in summer months for school-age children or for the entire population, vaccinating in summer months became least effective for reducing population mortality. Similarly, when increasing contact annually every February, vaccinating in December became advantageous to maximize population immunity prior to high social mixing and its resulting high influenza transmission. These differences became more pronounced as the magnitude of change social contact increased (Figure S11). Under the largest decrease in school-based contact, the 10-19 age group was no longer the clear optimal group to target for vaccination at low vaccine supplies; the 30-39 group became an advantageous target. Under all other scenarios, however, this group remained most advantageous to target for vaccination (Figure S12).

The results of these last sensitivity analyses with changing contact patterns also show the sensitivity of our model to perturbations in parameterization. Figure S11 shows that, without any vaccination, changing the contact matrix, and therefore transmission, can lead to substantial changes in average annual mortality. While the relative trends seen in Figure S11 are illustrative of the effects of time-varying contact patterns on the timing of vaccine administration, changing model parameters directly related to influenza transmission without changing other parameters accordingly will substantially change out model's estimated influenza burden. These sensitivity analyses also introduce transmission patterns through contact patterns that change based on the calendar year, so these results have meaningful interpretations with regards to the calendar year.

Supplementary tables

Table S1. Parameters assumed, taken from literature, and estimated for mathematical model, including references for values or methods of estimation.

Parameter	Value	Reference or method of estimation
transmission parameter for A/H1, β_{0H1}	Estimated in parameter search	Middle value after drawing 1. $\mu_\beta \sim U(0.15, 0.70)$ 2. 3 Draws of $N(\mu_\beta, 0.01)$
transmission parameter for A/H3, β_{0H3}	Estimated in parameter search	Highest value after drawing 1. $\mu_\beta \sim U(0.15, 0.70)$ 2. 3 Draws of $N(\mu_\beta, 0.01)$
transmission parameter for B, β_{0B}	Estimated in parameter search	Lowest value after drawing 1. $\mu_\beta \sim U(0.15, 0.70)$ 2. 3 Draws of $N(\mu_\beta, 0.01)$
Times of peak transmission, φ_k	Estimated in parameter search	Drawn from distributions estimated previously [2]; spacings between peaks are distributed $N(376, 150)$; (sub)type selected randomly for each peak
Cross immunity across (sub)types, σ_{ij}	A/H1 and A/H3: 30% A/H1 and B: 27% A/H3 and B: 17% Assumed symmetric, assumed 100% for σ_{ii}	[1]
Duration of increased transmission (days), δ	Estimated in parameter search	Drawn from $U(45, 180)$
Magnitude of increased transmission (multiplier), α	Estimated in parameter search	Drawn from $U(0, 0.5)$
Duration between case importations	Estimated in parameter search	Drawn from $U(90, 365)$
Duration of infection (days), ν	5	Assumed
Hospitalization fraction among cases, all (sub)types, h_a	0-9: 0.0048 10-19: 0.0033 20-29: 0.0056 30-39: 0.0056 40-49: 0.0056 50-59: 0.0106 60-69: 0.0460 70+: 0.0909	[4]

Table S1 cont.

Death fraction among hospitalizations, all (sub)types, d_a	0-9: 0.0094 10-19: 0.0125 20-29: 0.0289 30-39: 0.0289 40-49: 0.0289 50-59: 0.0574 60-69: 0.0780 70+: 0.1041	[4]
Vaccine effectiveness, ξ	0.5	Assumed 0.5 for effectiveness against infection, hospitalization if infected, and death if hospitalized [10–14]
Duration of infection-induced immunity (days), ρ^{-1}	Estimated in parameter search	Drawn from U(180, 1460)
Duration of vaccine-induced immunity, ρ_v^{-1}	270 days	Assumed [15]

Table S2. Changes in average annual mortality under single-age prioritization strategies compared to proportional vaccine allocation. For each vaccine supply and age group prioritized, the average relative change in mortality is shown as well as the median (IQR) relative change in mortality among the 50 parameter sets.

Supply	Age Group	Relative change in mortality averaged across parameterizations	Median (IQR) relative change in mortality among all parameterizations
10%	0-9	-0.40%	0.4% (-5.1 - 3.7%)
	10-19	-11.50%	-11.6% (-15.2 - -7.4%)
	20-29	-3.80%	-4.4% (-5.6 - -2.1%)
	30-39	-5.90%	-6.2% (-7.8 - -4.9%)
	40-49	-1.70%	-1.5% (-4.2 - 1%)
	50-59	3.40%	2.9% (-1.3 - 8.6%)
	60-69	-4.60%	-5.3% (-8.5 - -0.3%)
	70+	-5.80%	-6.8% (-8.9 - -2.3%)
20%	0-9	10.70%	8.9% (6.7 - 15.5%)
	10-19	1.80%	0.5% (-4.2 - 8.9%)
	20-29	6.40%	6.1% (4.9 - 7.8%)
	30-39	5.30%	4.7% (3.8 - 7.3%)
	40-49	6.10%	5.1% (3.3 - 8.5%)
	50-59	6.80%	4.7% (2.8 - 12.1%)
	60-69	-1.50%	-3.1% (-5.6 - 3.1%)
	70+	-2.30%	-2.8% (-5.5 - 1.1%)
30%	0-9	13.50%	12.7% (10 - 18.7%)
	10-19	-4.90%	-4.2% (-17.7 - 2.7%)
	20-29	9%	8.9% (6.9 - 11.6%)
	30-39	8.40%	8.5% (5.6 - 11.5%)
	40-49	9.10%	8.6% (6.7 - 11.3%)
	50-59	9.20%	8.3% (5.1 - 16.8%)
	60-69	1.90%	0.7% (-2.7 - 9.2%)
	70+	1%	0.1% (-2.6 - 7.1%)
40%	0-9	17.80%	18.8% (15.8 - 24.1%)
	10-19	-5.60%	-10.1% (-26.3 - 2%)
	20-29	14.30%	13.4% (10.3 - 17.6%)
	30-39	14.90%	14% (9 - 18.8%)
	40-49	14.80%	15.7% (12.1 - 18.8%)
	50-59	13.70%	13.5% (9.2 - 26.8%)
	60-69	6.60%	7% (1.3 - 22.2%)
	70+	4.10%	4.5% (0.3 - 15.2%)

Table S2 cont.

50%	0-9	19.10%	19.5% (13.3 - 26%)
	10-19	-16.90%	-16.7% (-43.4 - -4.1%)
	20-29	15.10%	13.4% (6.7 - 17.8%)
	30-39	19.10%	16% (5.8 - 22.1%)
	40-49	18.60%	18.9% (12.2 - 22.9%)
	50-59	19.10%	20.8% (9.5 - 31.2%)
	60-69	13.10%	14.6% (3.9 - 28.8%)
	70+	8.70%	10.4% (3.9 - 18.6%)
60%	0-9	13.90%	15% (4.3 - 20%)
	10-19	-23.30%	-15.3% (-48.1 - -3.9%)
	20-29	12.50%	7.8% (0 - 14.5%)
	30-39	18.90%	11.6% (-0.8 - 19.1%)
	40-49	17.50%	15.5% (2.3 - 21.1%)
	50-59	18.30%	19.3% (5.2 - 35.7%)
	60-69	14.80%	14.8% (4.3 - 34.1%)
	70+	8.90%	10.4% (1 - 22.6%)
70%	0-9	9.70%	2.8% (0.9 - 12.8%)
	10-19	-18.40%	-5.5% (-25.1 - -1.2%)
	20-29	9.80%	0% (0 - 6%)
	30-39	14.80%	-0.3% (-0.7 - 10.7%)
	40-49	12.80%	1% (0.1 - 15%)
	50-59	14.30%	6.1% (0.9 - 23.1%)
	60-69	12.30%	5.1% (0.4 - 22.8%)
	70+	7.60%	2.4% (0.1 - 14.7%)
80%	0-9	1.80%	0.7% (0.4 - 2%)
	10-19	-8.20%	-1.2% (-5.9 - -0.5%)
	20-29	0.80%	0% (-0.1 - 0%)
	30-39	1.40%	-0.2% (-0.6 - -0.1%)
	40-49	2.10%	0.1% (0 - 0.2%)
	50-59	4.80%	0.7% (0.4 - 3.4%)
	60-69	4.50%	0.5% (0.1 - 3.5%)
	70+	2.70%	0.2% (0 - 2.1%)
90%	0-9	0.70%	0.3% (0.2 - 0.5%)
	10-19	-2.30%	-0.4% (-0.7 - -0.2%)
	20-29	-0.20%	0% (0 - 0%)
	30-39	-0.90%	-0.1% (-0.4 - -0.1%)
	40-49	0.10%	0% (0 - 0.1%)
	50-59	1.20%	0.3% (0.1 - 0.5%)
	60-69	1%	0.1% (0 - 0.4%)
	70+	0.60%	0.1% (0 - 0.2%)

Supplementary Figures

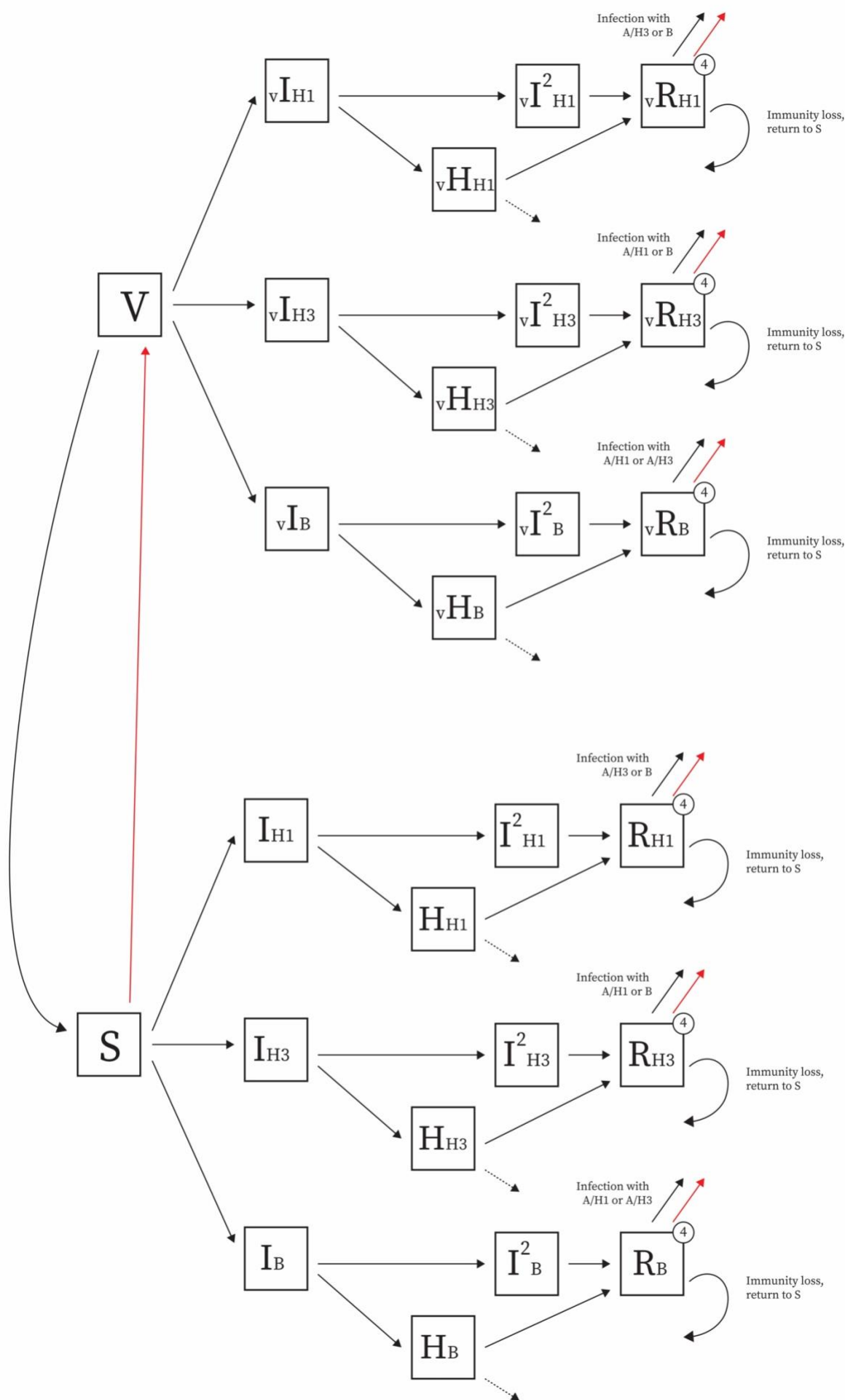


Figure S1. Model diagram used for analyses. This diagram represents the flow of compartments for each age group. Mixing across age groups is modeled based on previously estimated contact patterns. Compartments for Susceptible (S), Vaccinated (V), Infectious (I), second-stage infected (I²), Hospitalized (H), Recovered (R), and Dead (D) are present. Compartment labels preceded by a lowercase v indicate Infectious, Hospitalized, or Recovered after being vaccinated. Subscript H1, H3, and B denote the (sub)type of infection. The circled number 4 over the Recovered stages indicates the presence of four Recovered compartments, with reinfection from the other (sub)types possible in any of these stages. Red arrows indicate vaccination, moving populations into the Vaccinated class. This diagram is repeated for all eight age classes.

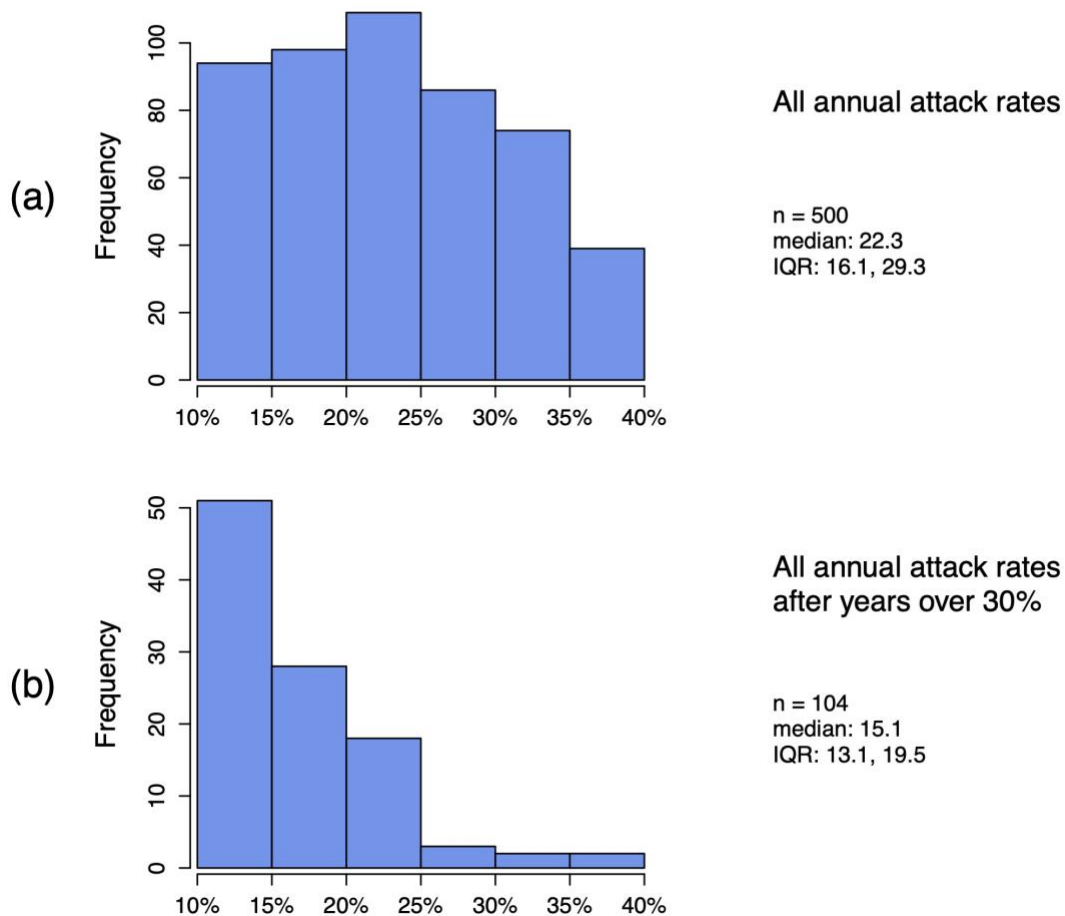


Figure S2. Distribution of annual attack rates from model simulations. (a) Distribution of ten annual attack rates for each of 50 model parameterizations ($n = 500$). (b) Distribution among the subset of attack rates occurring after a year in which the attack rate was over 30% ($n = 104$). Attack rates in years that follow years in which attack rates exceed 30% tend to be substantially lower compared to the set of all attack rates.

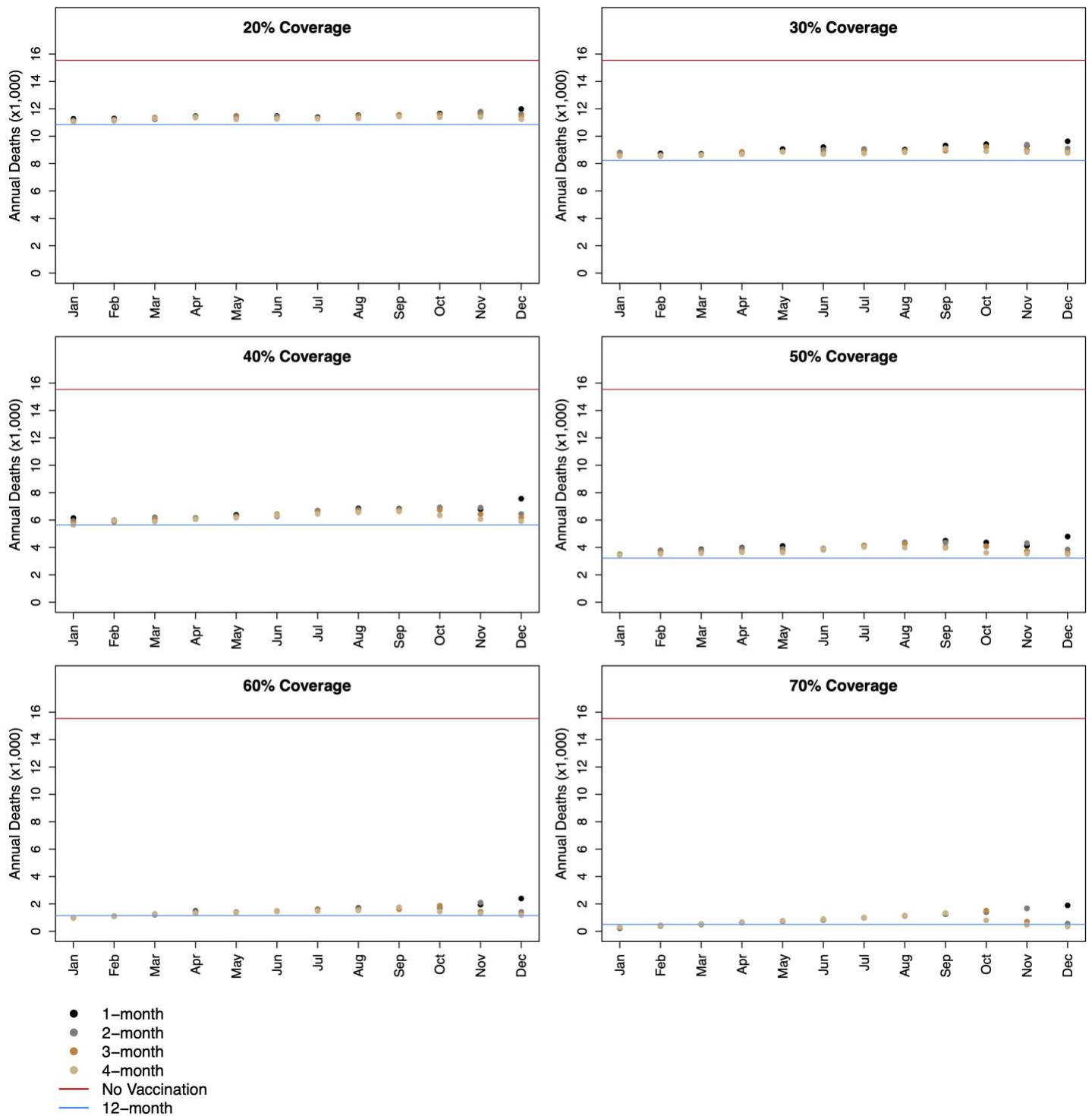


Figure S3. Results from selecting optimal timing of vaccines. Each panel shows the average annual mortality at a given vaccine coverage when beginning vaccination at the specified month and administering vaccines over a span of one to four months. Blue lines indicate average mortality when vaccinating continuously over 12 months. Under each start month and duration, population coverage over the calendar year is equal.

10% Supply

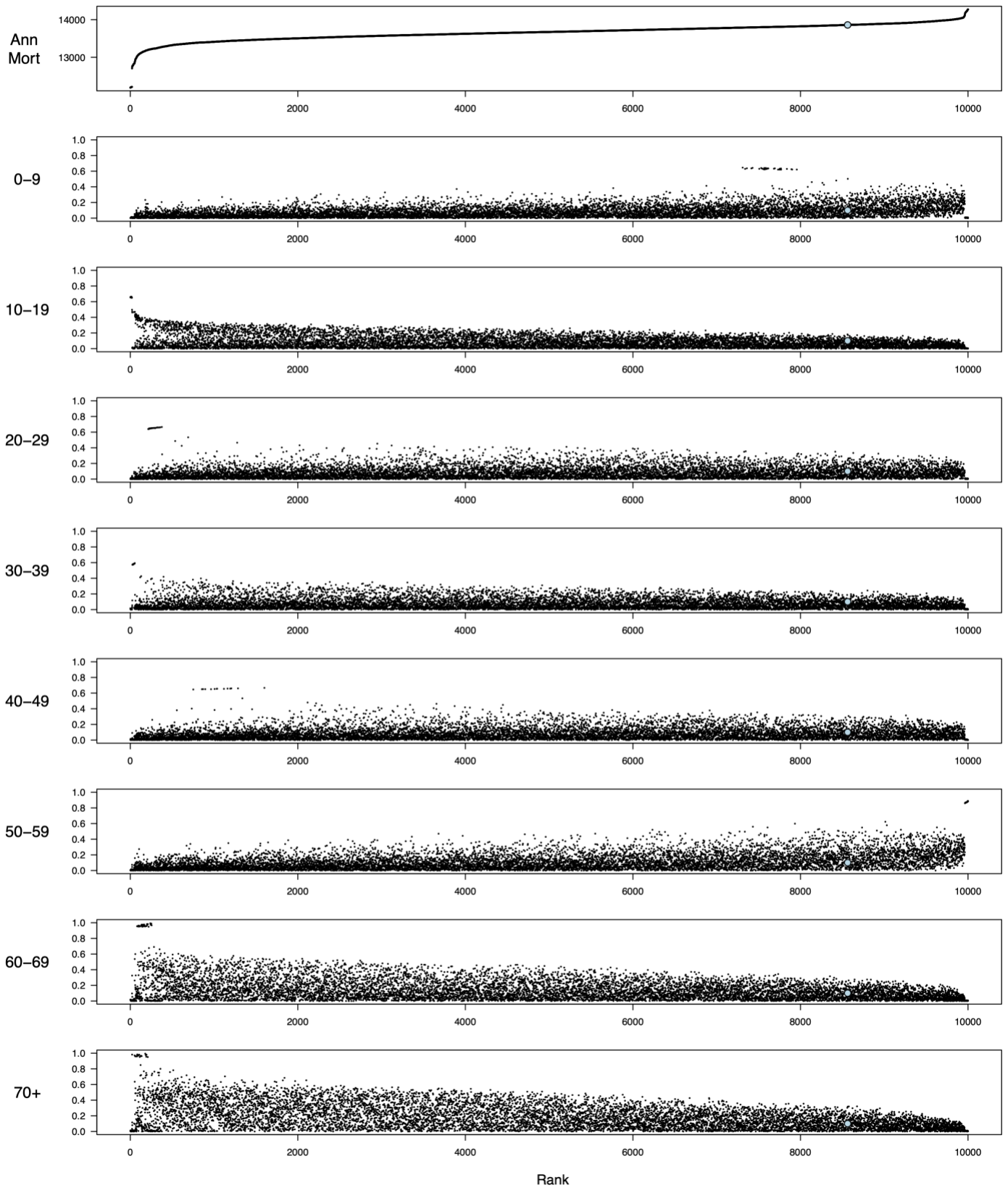


Figure S4. Rankings of evaluated vaccine allocations. Allocations are ranked by average annual population mortality. Each page represents a different vaccine supply. Blue dots represent an age-proportional vaccine allocation. Top panel: Average annual mortality for each vaccine allocation. Second through ninth panels: Vaccine coverages for each age group among the ranked vaccine allocations.

Figure S4 cont.

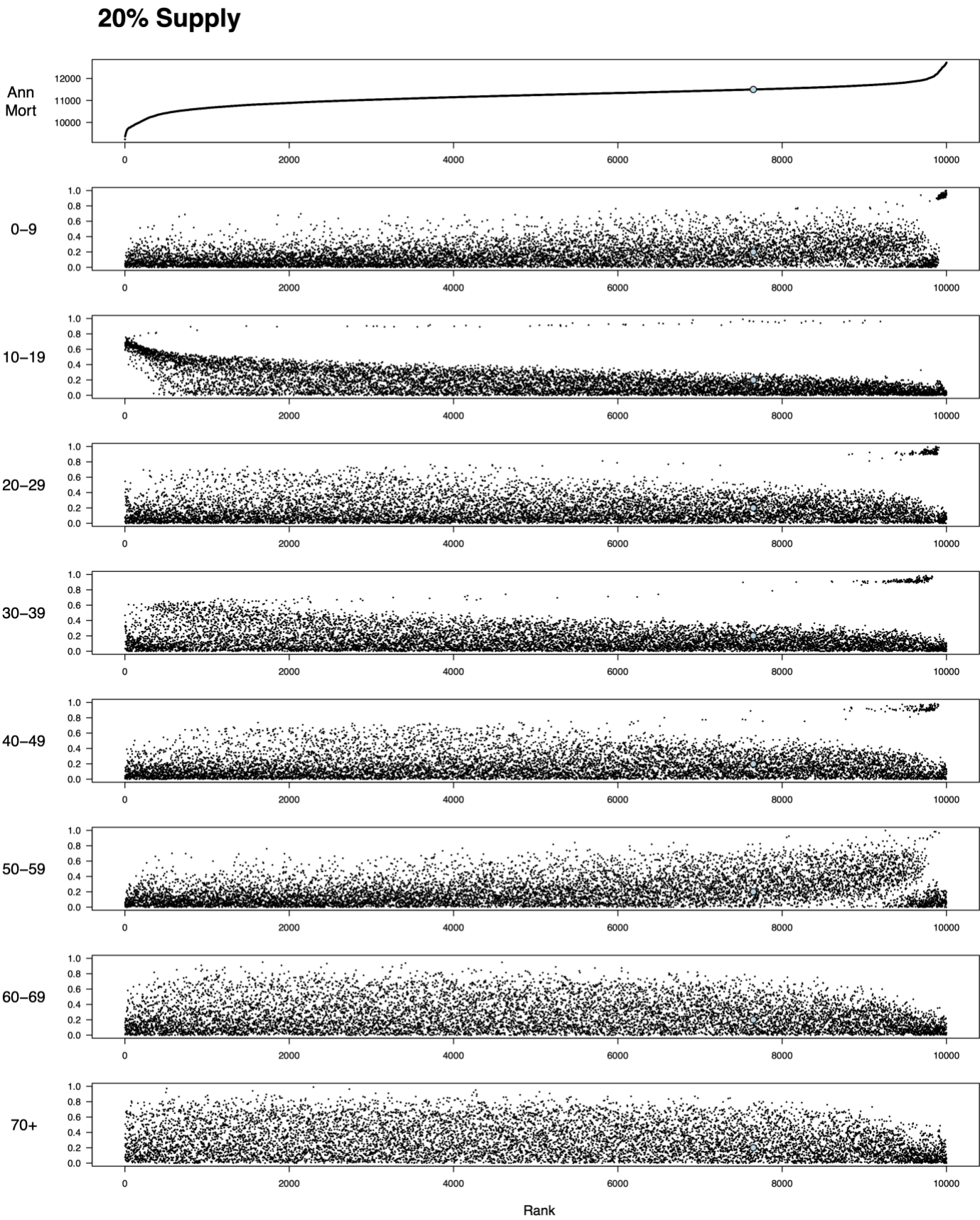


Figure S4 cont.

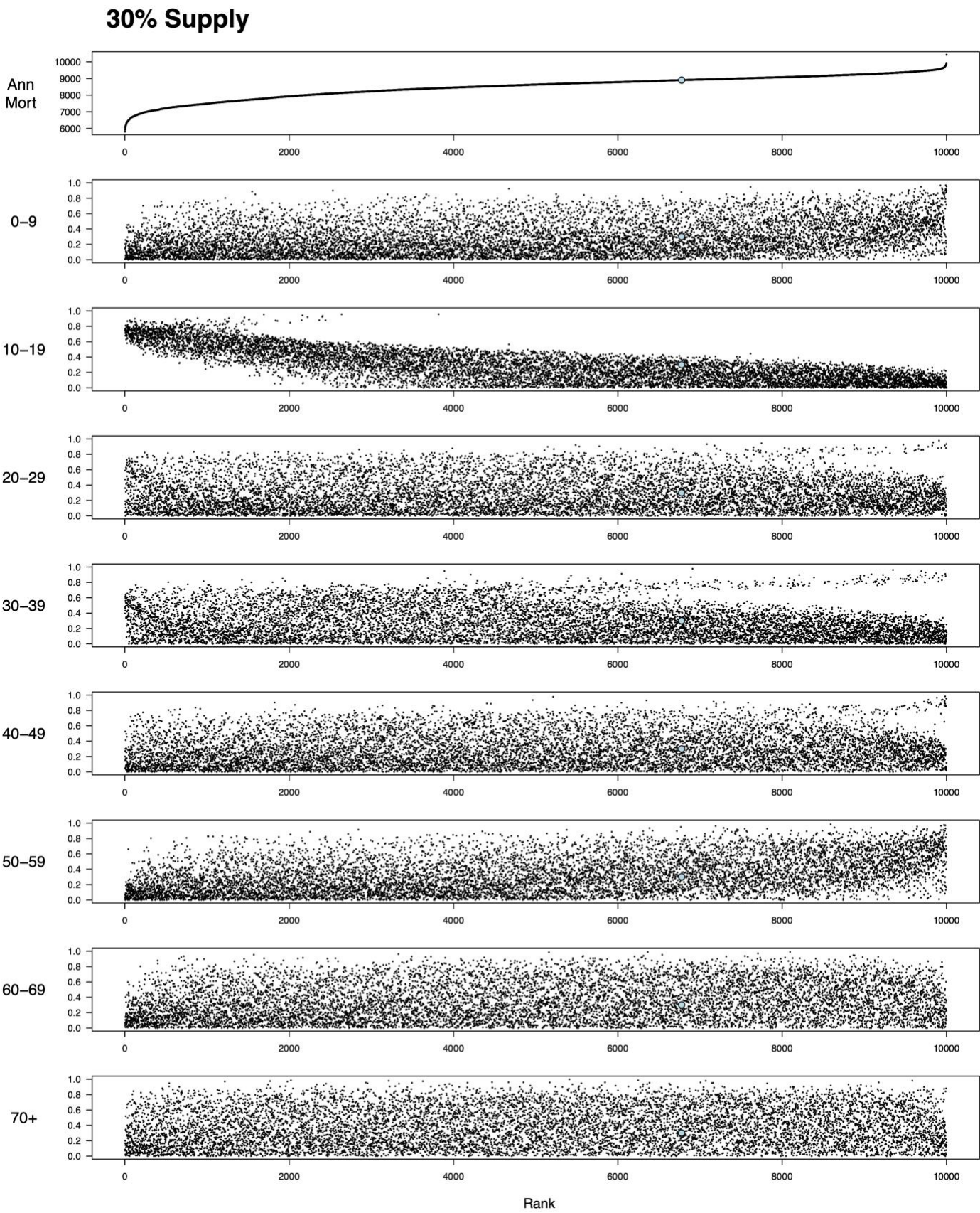


Figure S4 cont.

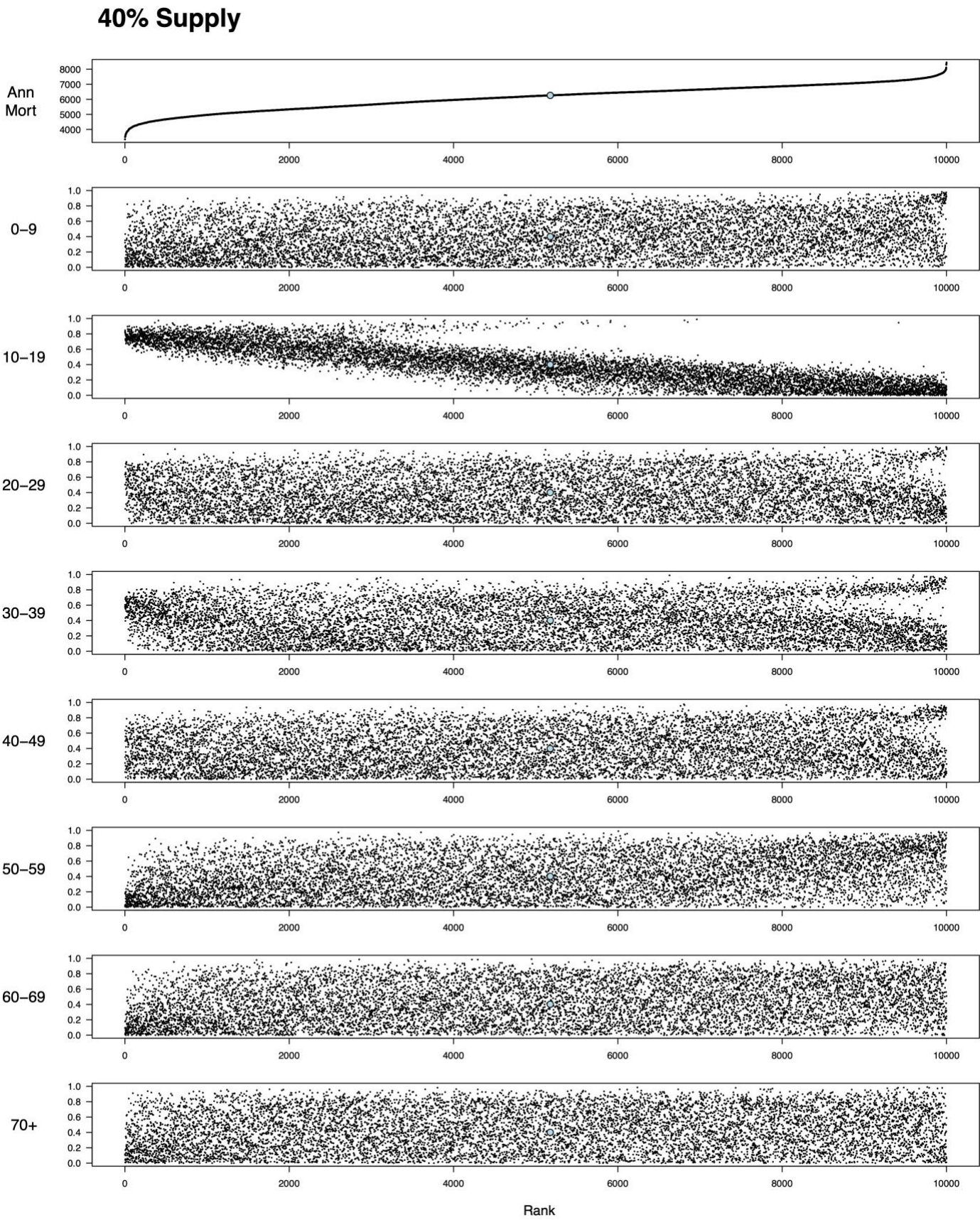


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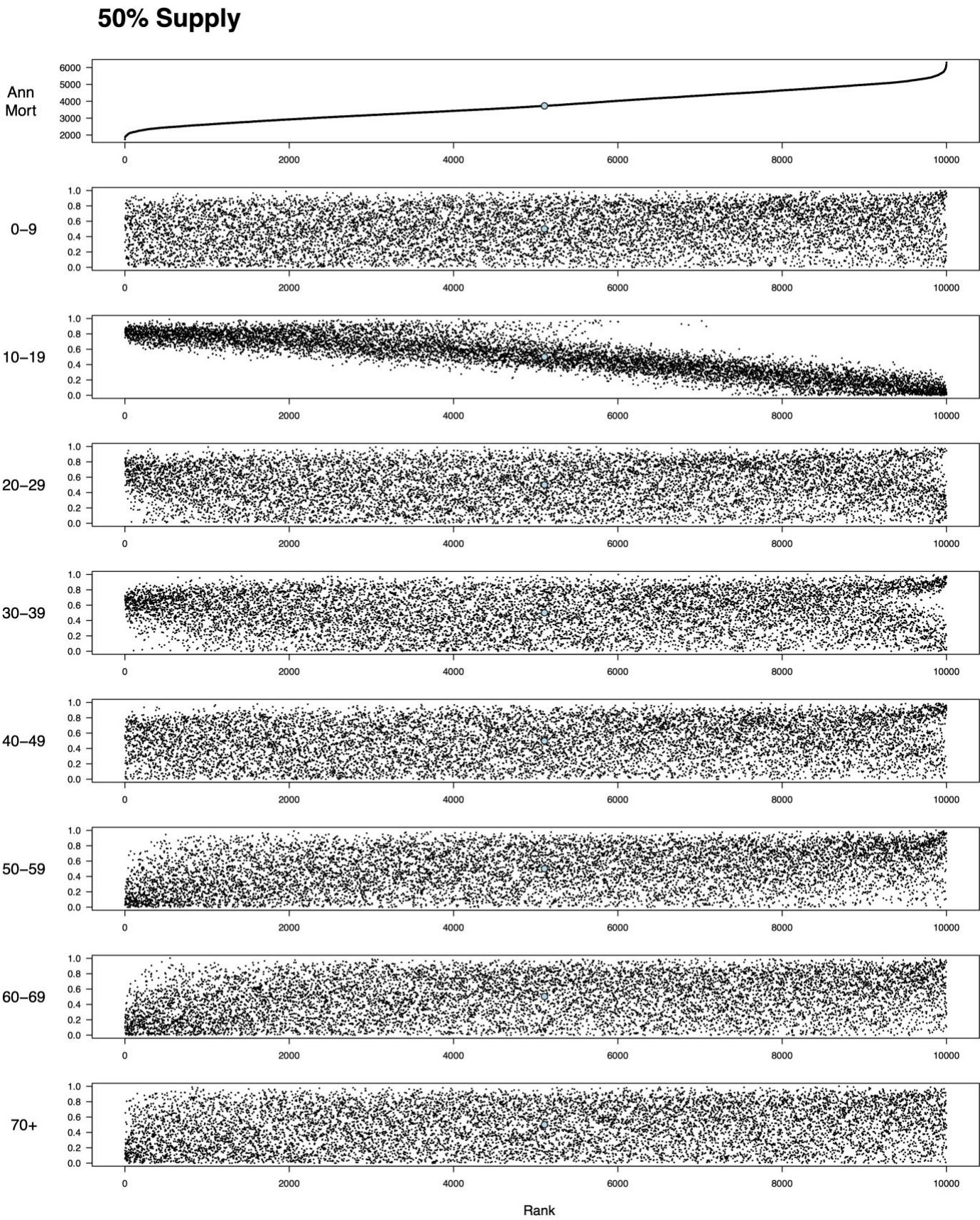


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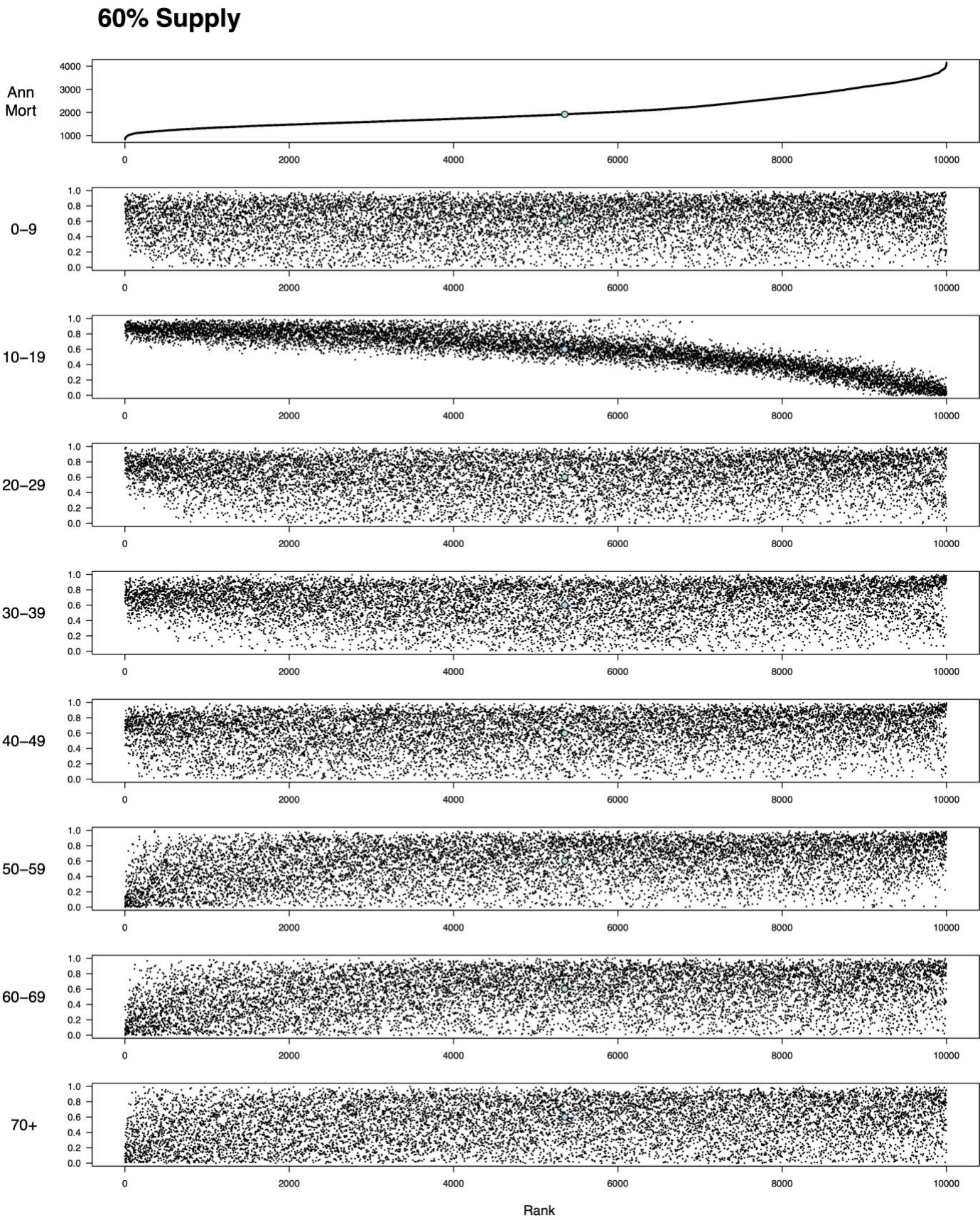


Figure S4 cont.

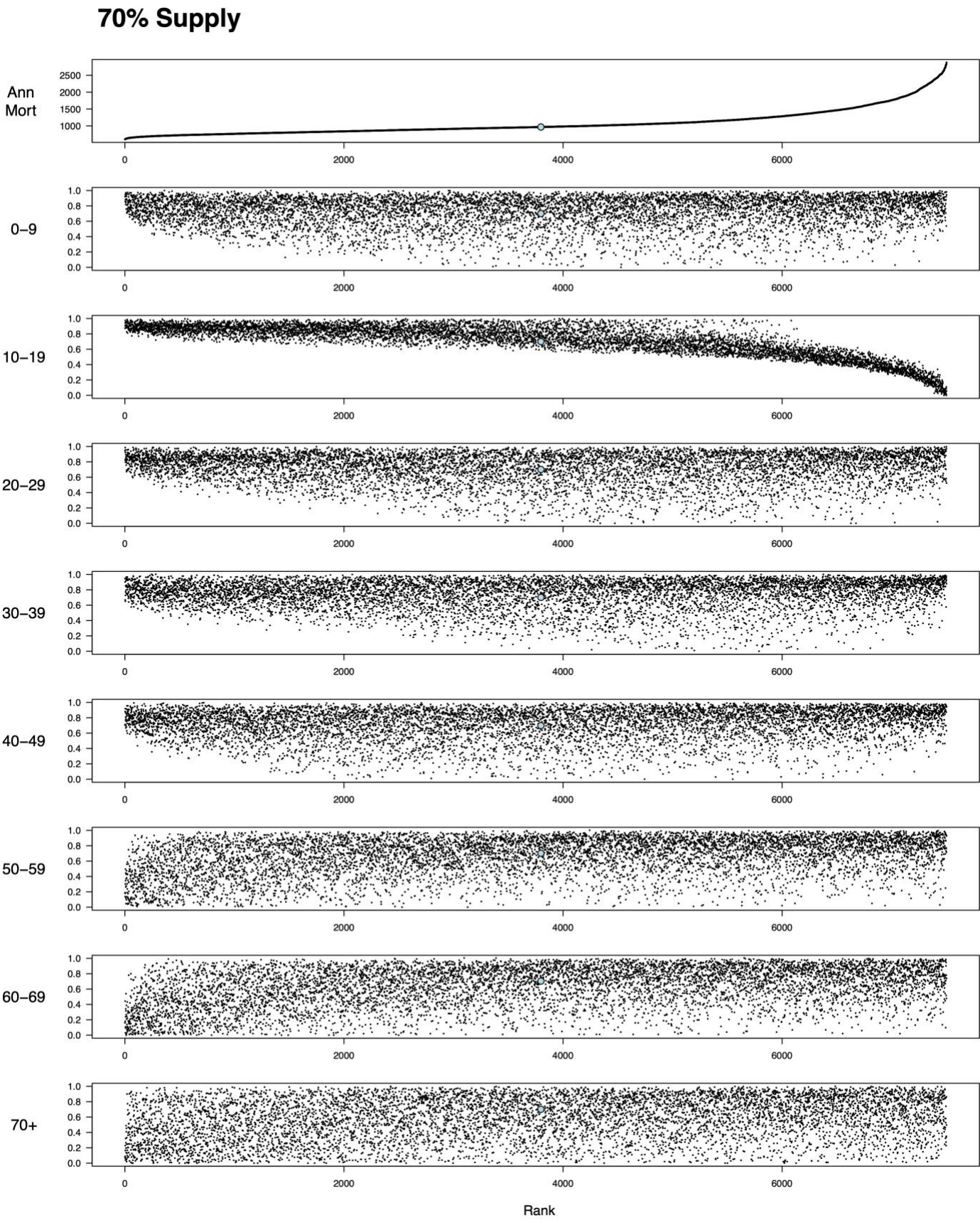


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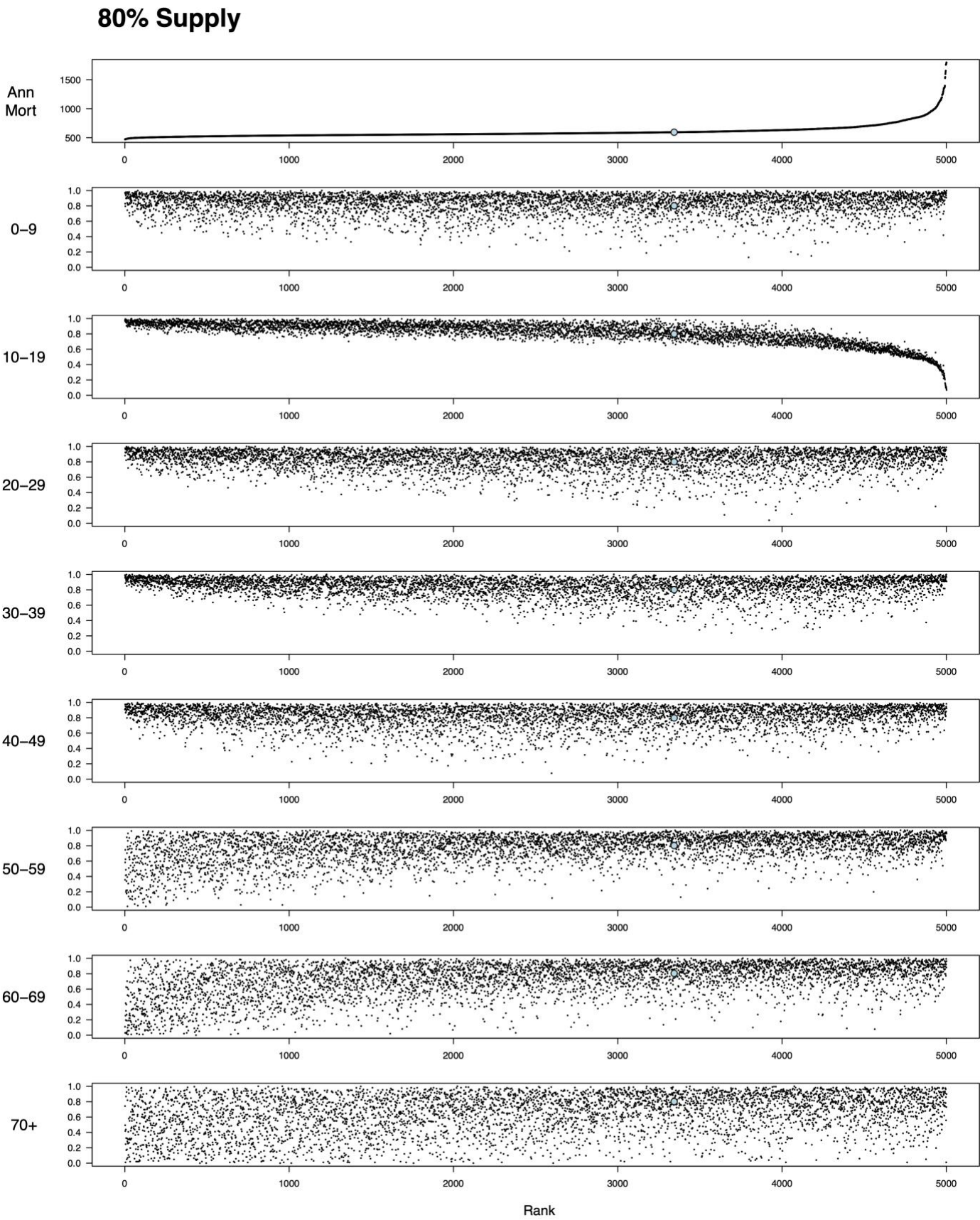
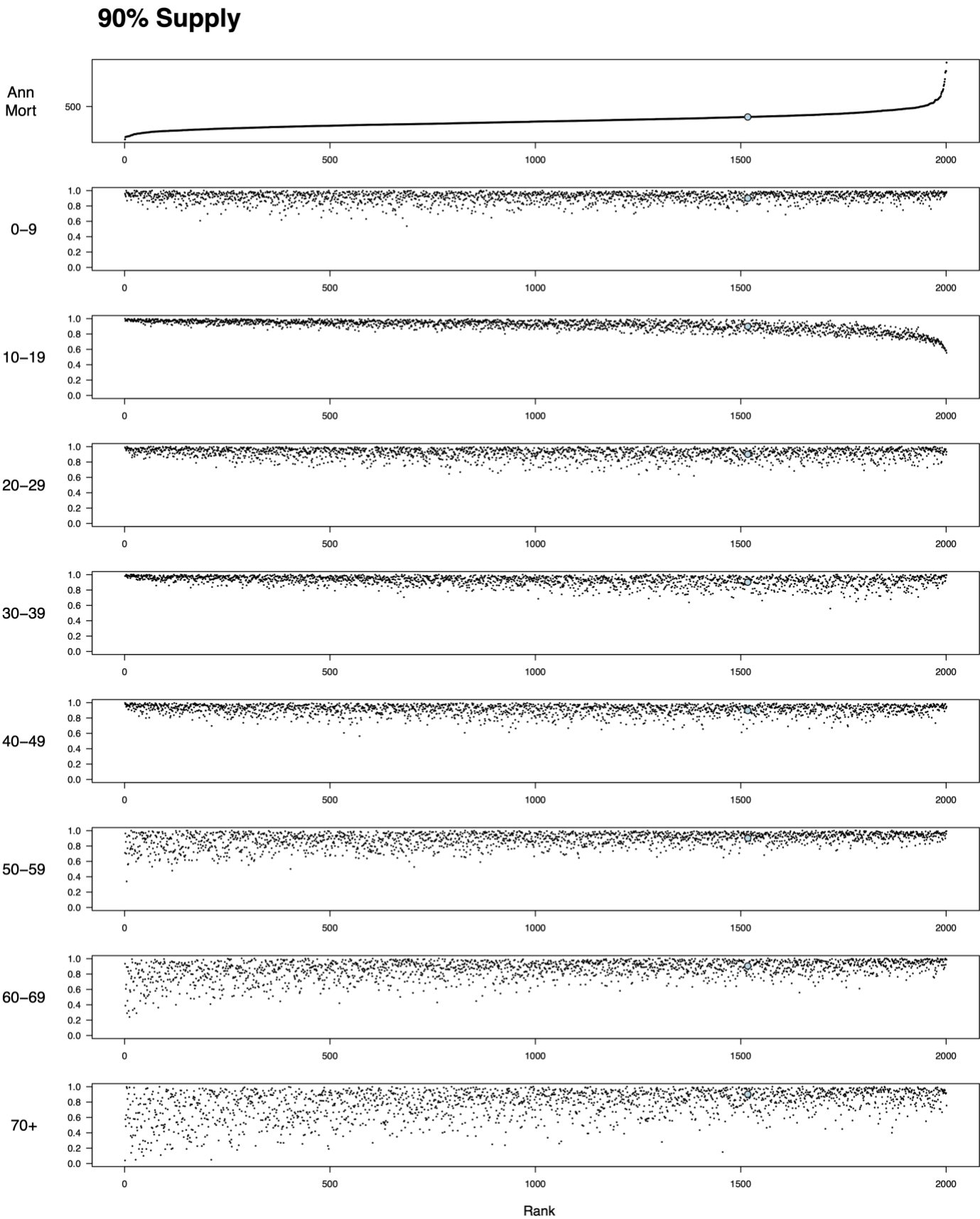


Figure S4 cont.



30% Vaccine Effectiveness

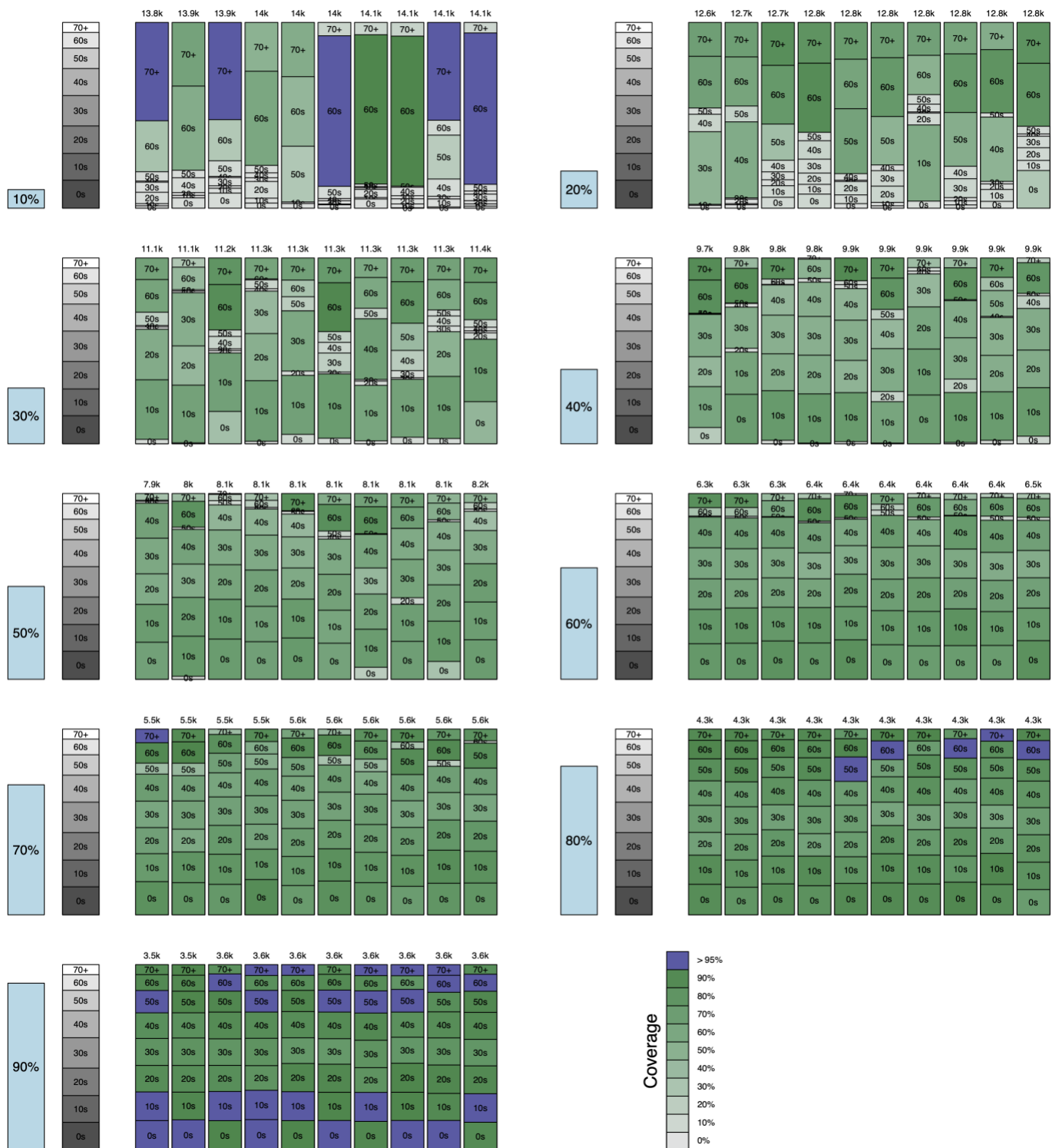


Figure S5. Optimal age-based vaccine allocations under different assumed vaccine effectiveness values. Mortality minimizing strategies based on vaccine supply if vaccine effectiveness against infection, hospitalization if infected, and death if hospitalized ranges between 30% and 70% are shown. Similar to Figure 4, blue bars indicate vaccine supply relative to the population, and relative proportions of the age groups in the general population of Vietnam are compared to the proportions of vaccines allocated to age groups. The ten strategies shown represent those associated with the lowest average annual mortality.

Figure S5 cont.

40% Vaccine Effectiveness

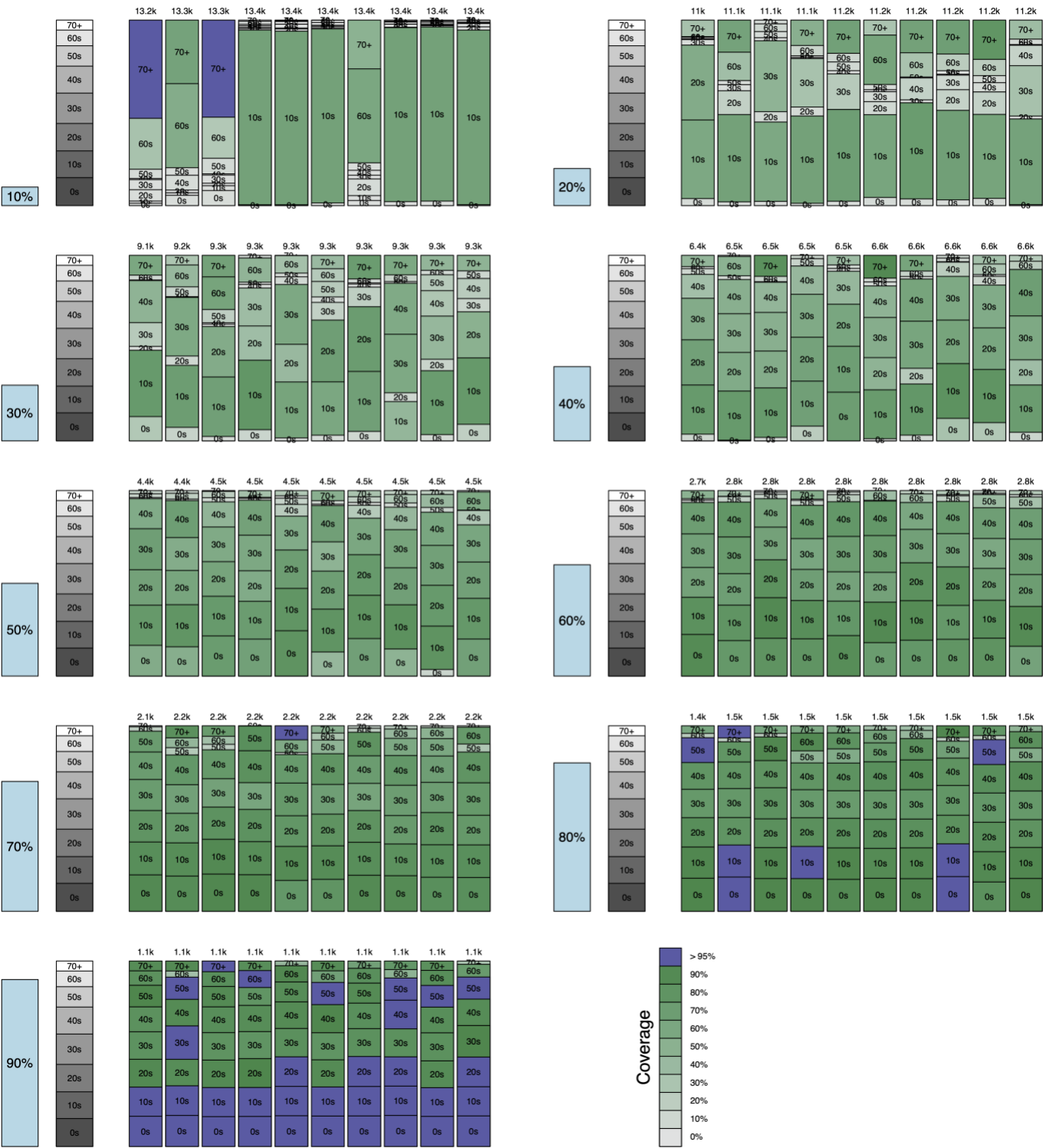


Figure S5 cont.

50% Vaccine Effectiveness

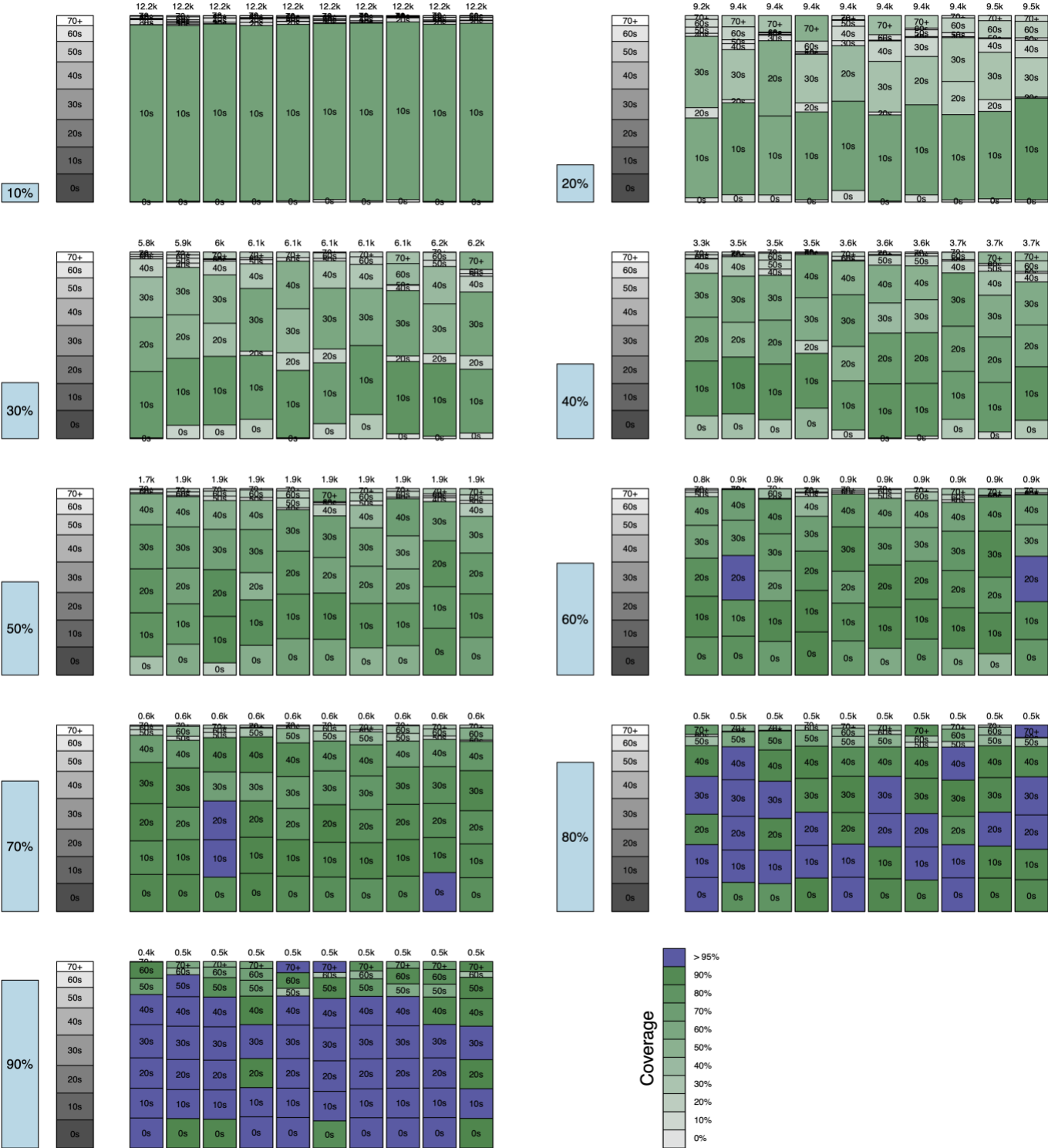


Figure S5 cont.

60% Vaccine Effectiveness

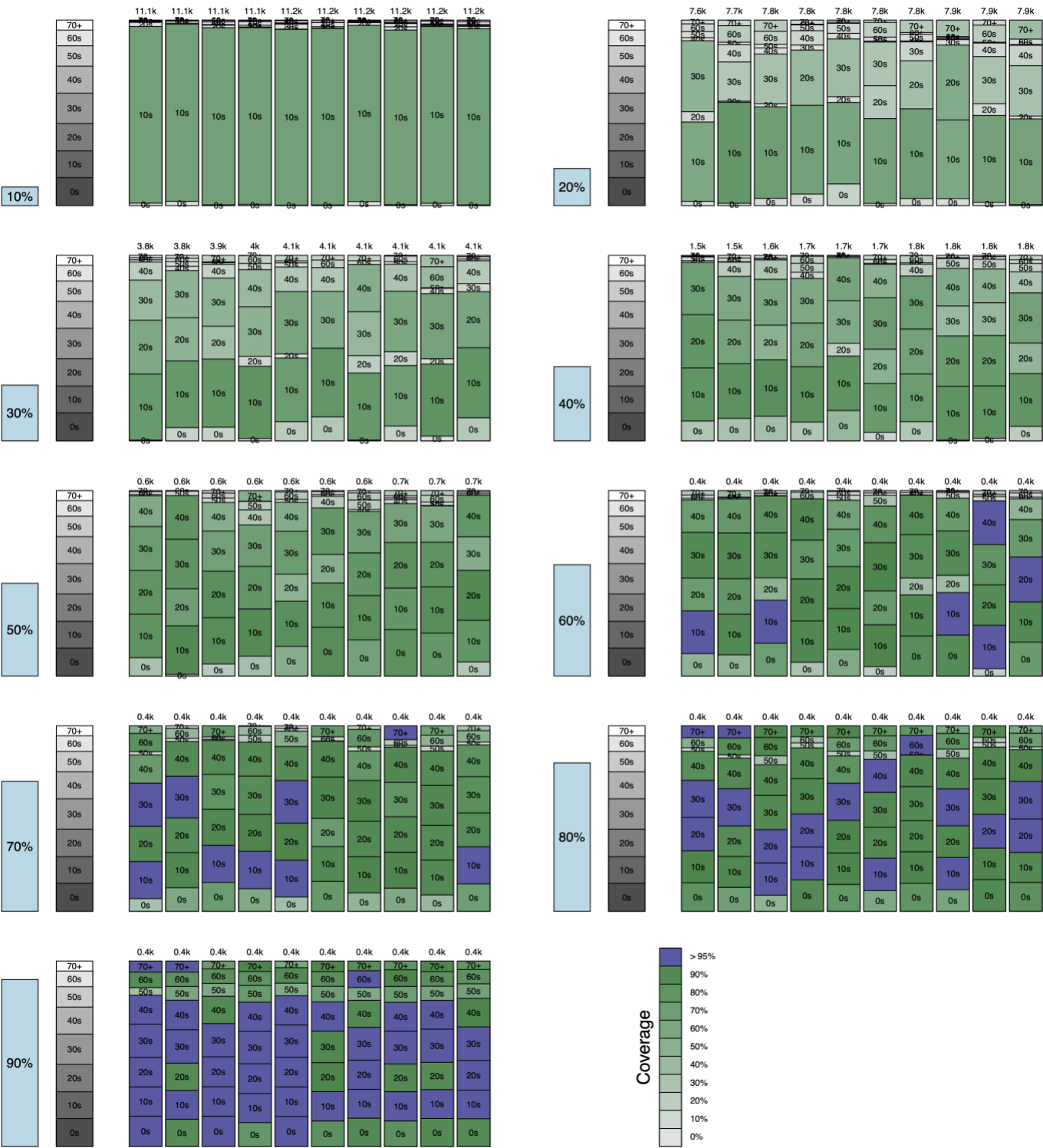
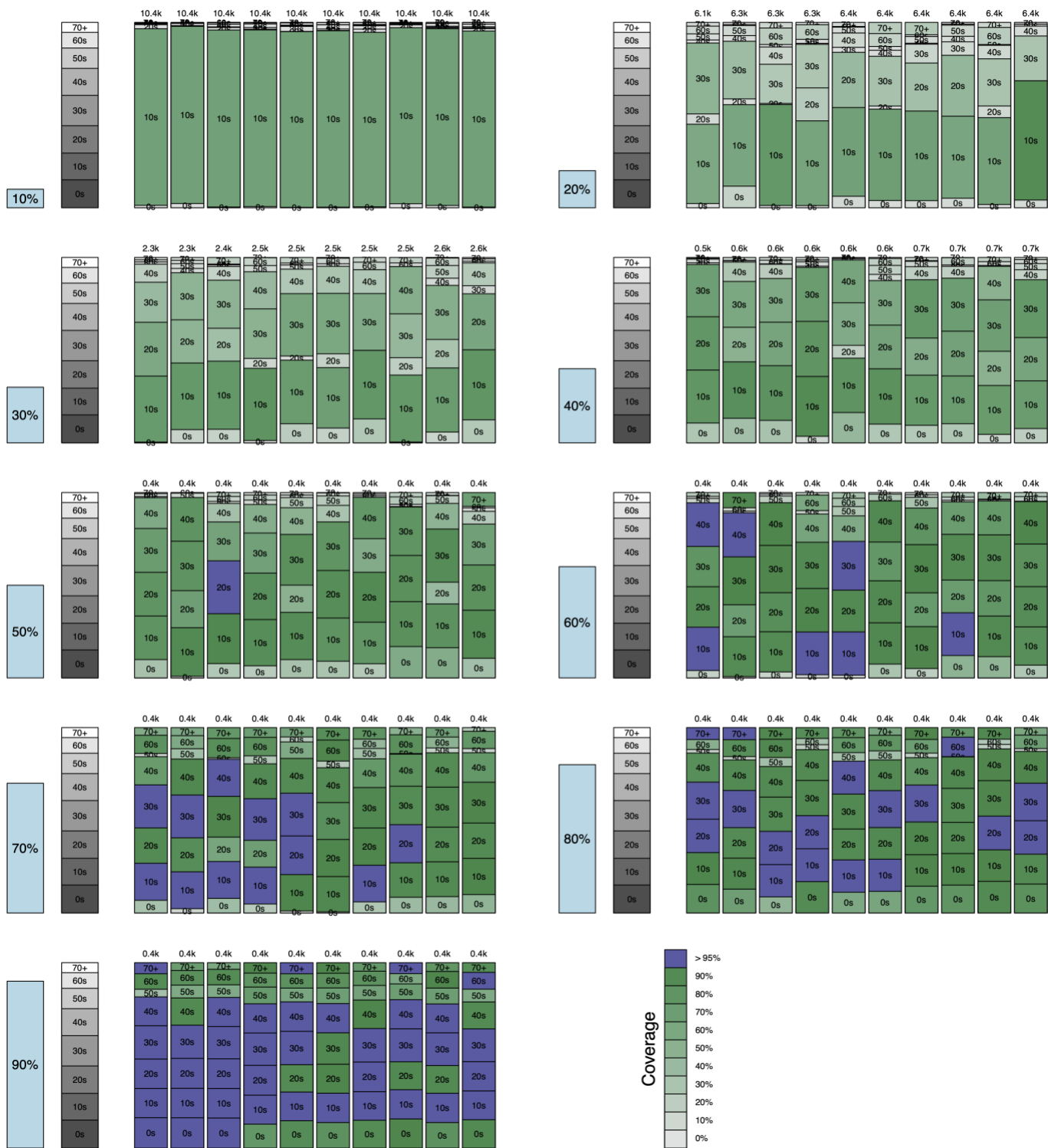


Figure S5 cont.

70% Vaccine Effectiveness



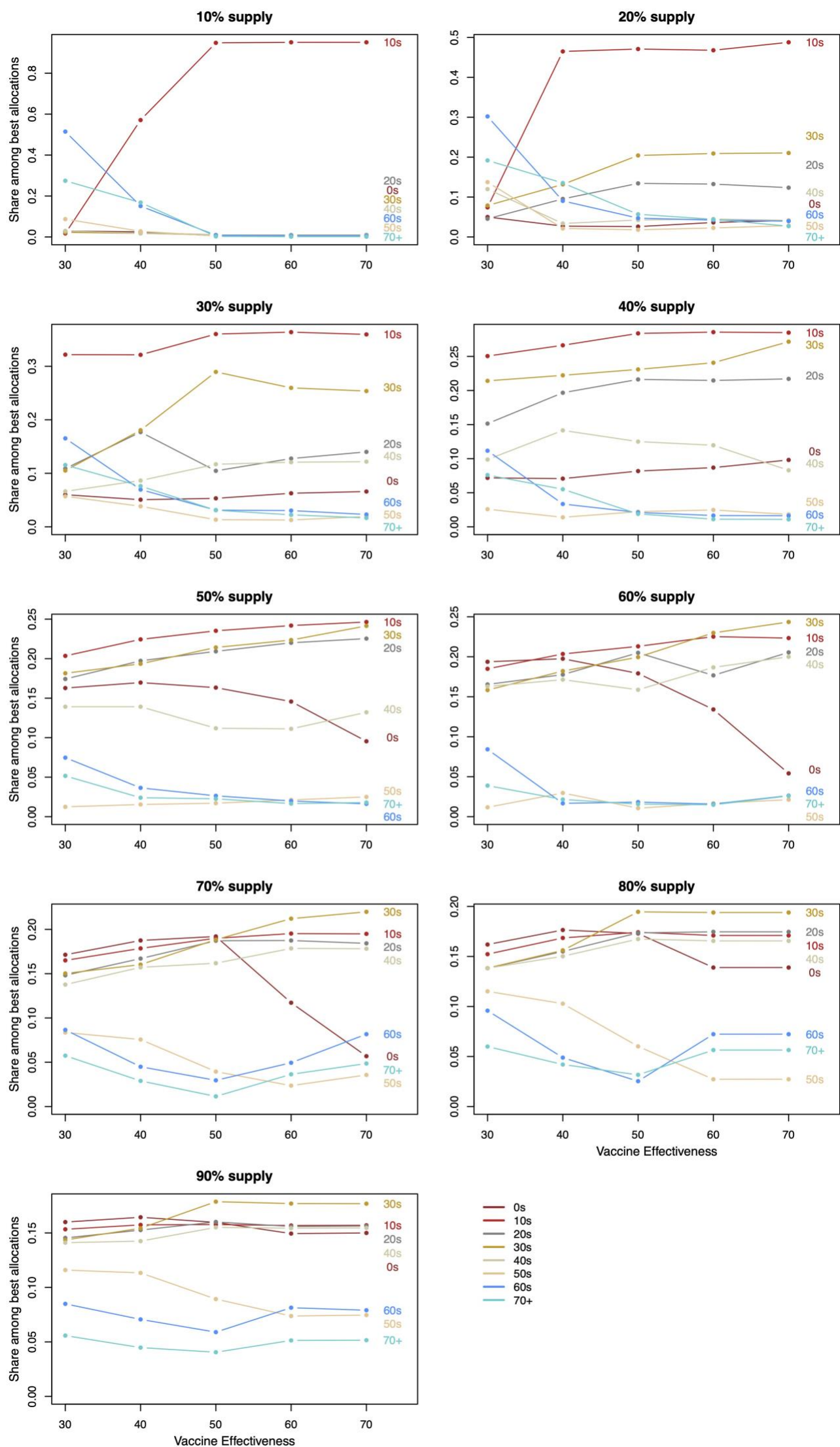


Figure S6. Shares of age groups comprising the set of ten mortality-minimizing vaccine allocations under different assumed vaccine effectiveness values across vaccine supplies. The average proportion of vaccines allocated to each age group among the vaccine allocations that lead to lowest average annual mortality are shown, by vaccine supply, for each assumed vaccine effectiveness to show how the most effective distributions of vaccines changes based on effectiveness.

180-day Immune Duration

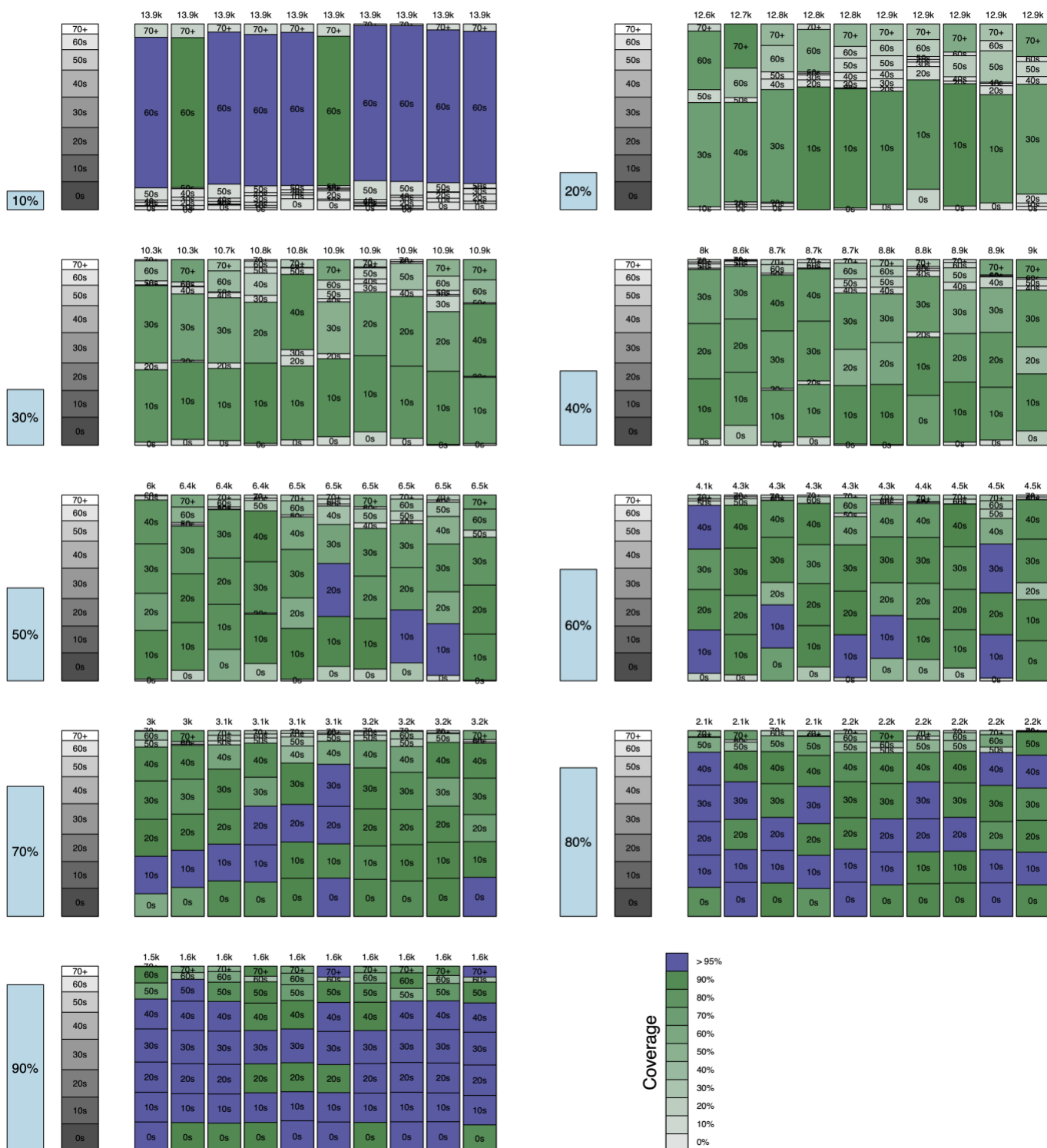


Figure S7. Optimal age-based vaccine allocations under different assumed vaccine-induced immunity durations. Mortality minimizing strategies based on vaccine supply if immune duration ranges between 180 days and 360 days are shown. Similar to Figure 4, blue bars indicate vaccine supply relative to the population, and relative proportions of the age groups in the general population of Vietnam are compared to the proportions of vaccines allocated to age groups. The ten strategies shown represent those associated with the lowest average annual mortality.

Figure S7 cont.

210-day Immune Duration

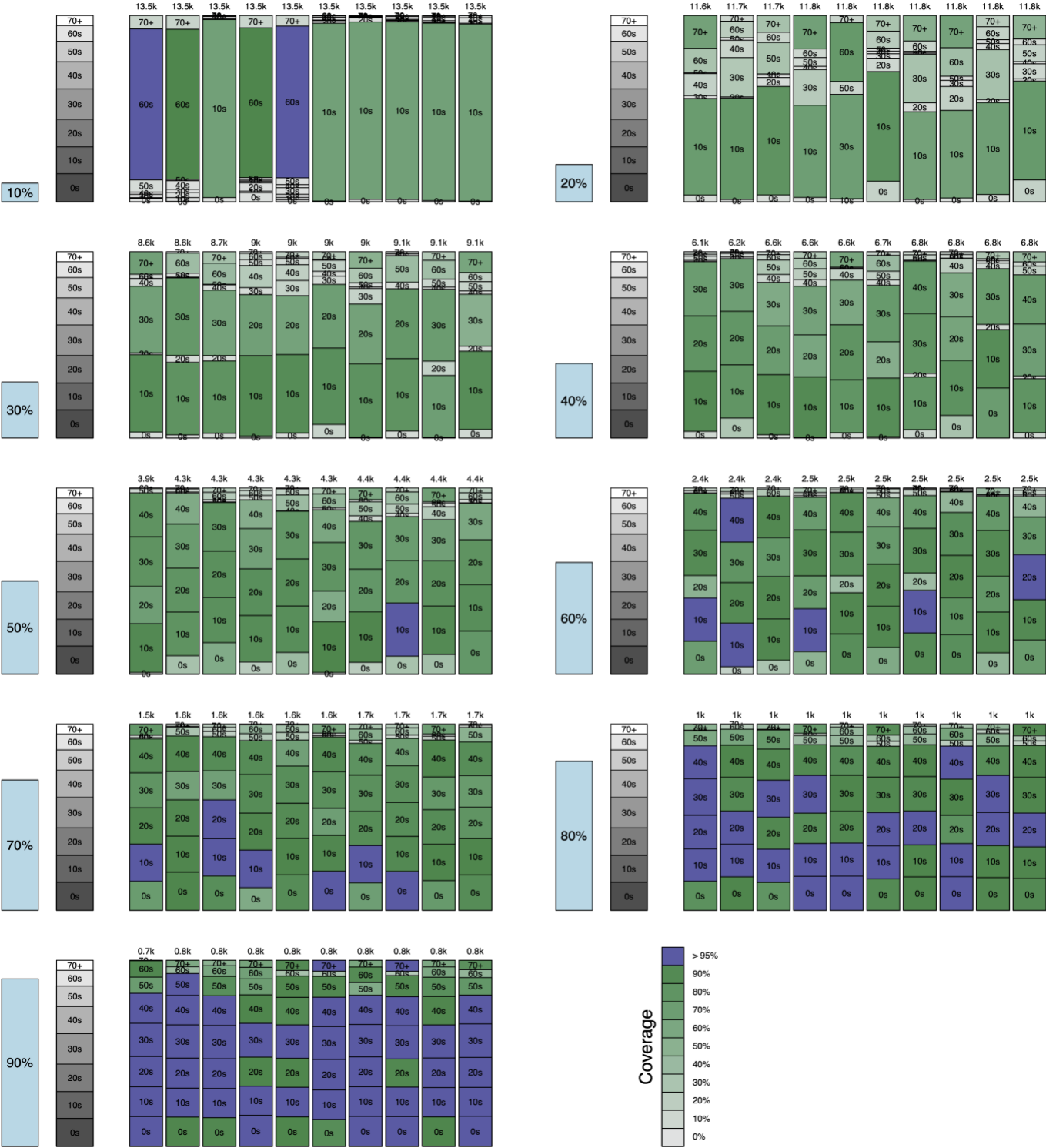


Figure S7 cont.

240-day Immune Duration

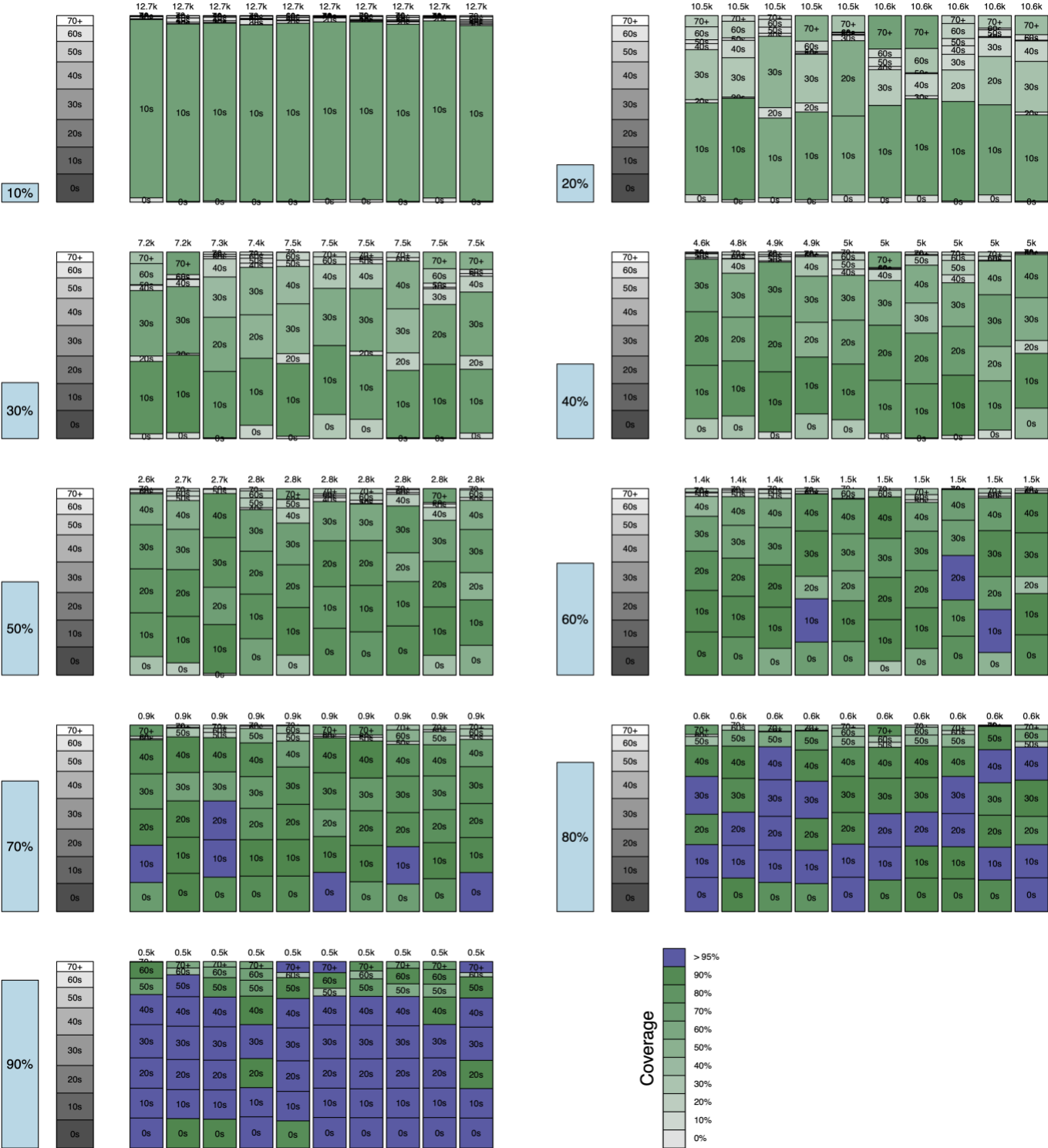


Figure S7 cont.

270-day Immune Duration

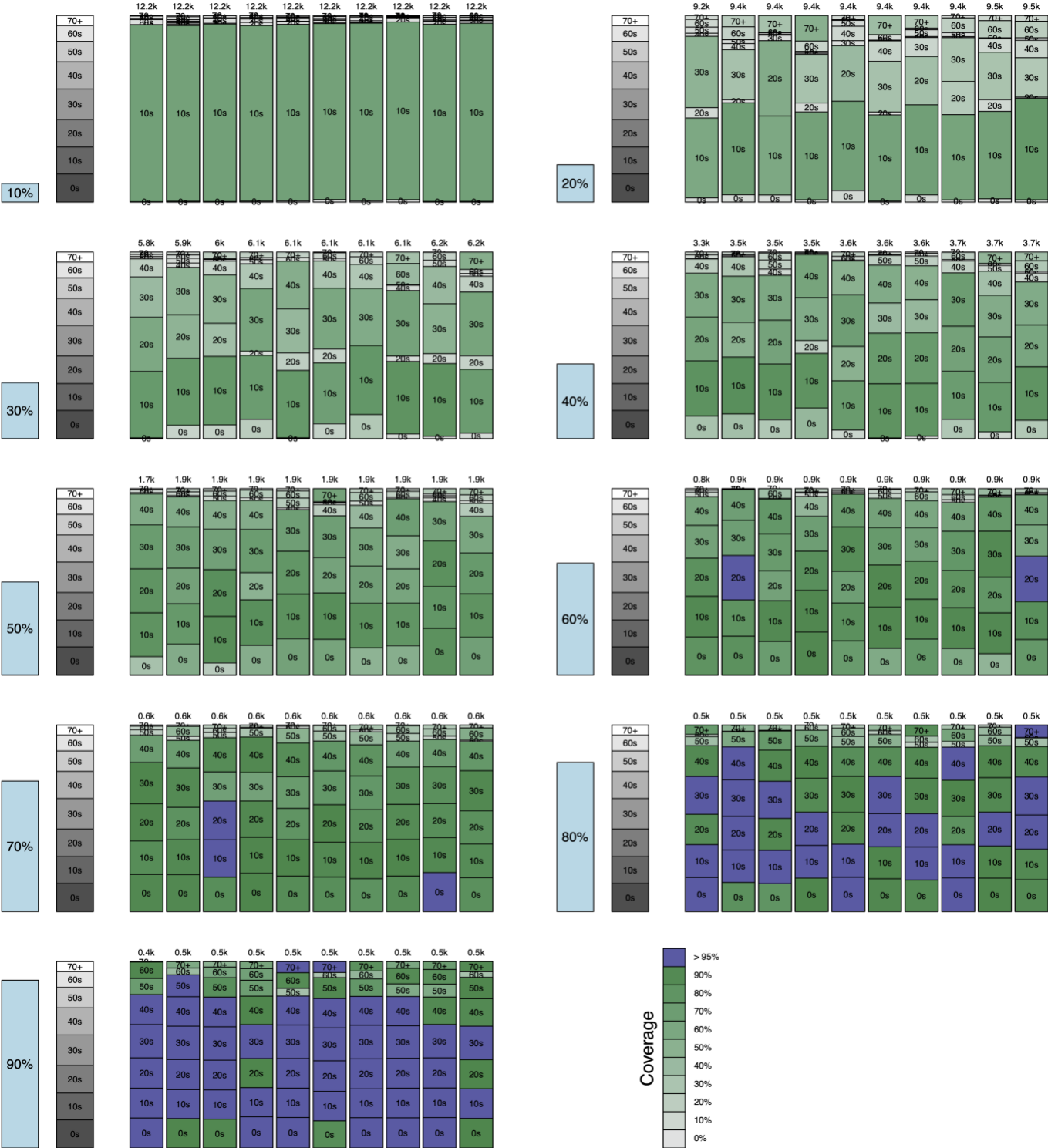


Figure S7 cont.

300-day Immune Duration

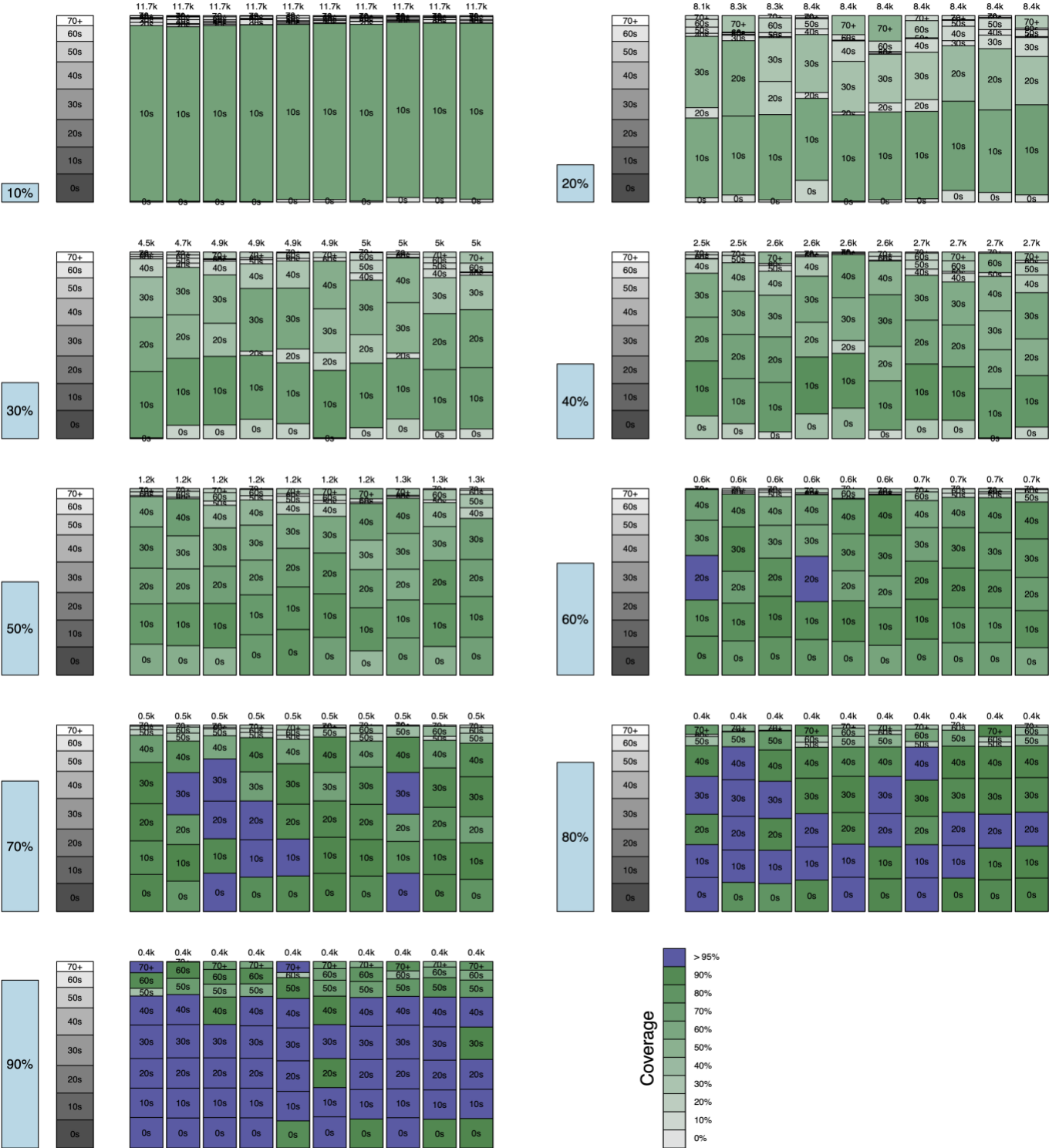


Figure S7 cont.

330-day Immune Duration

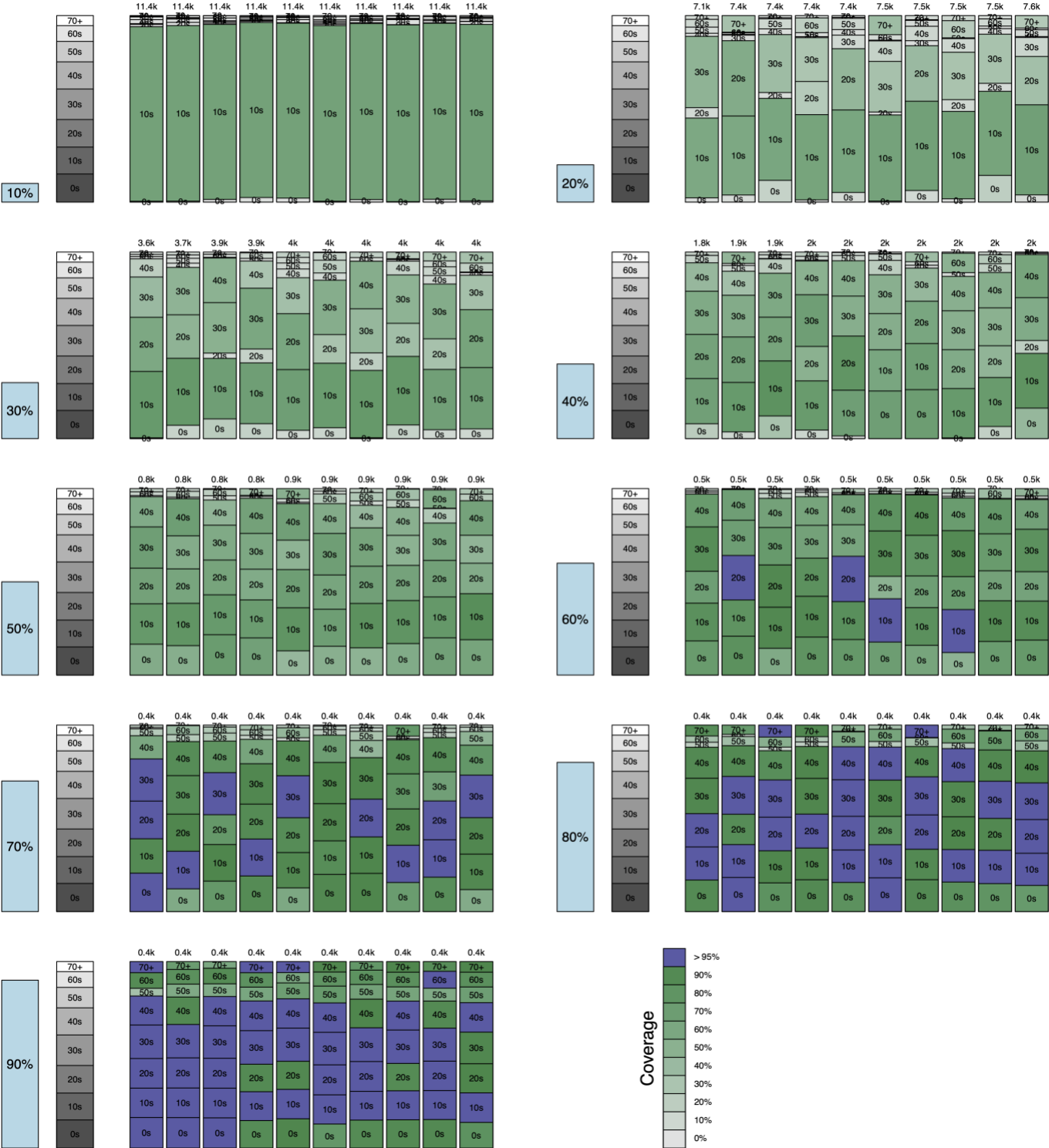
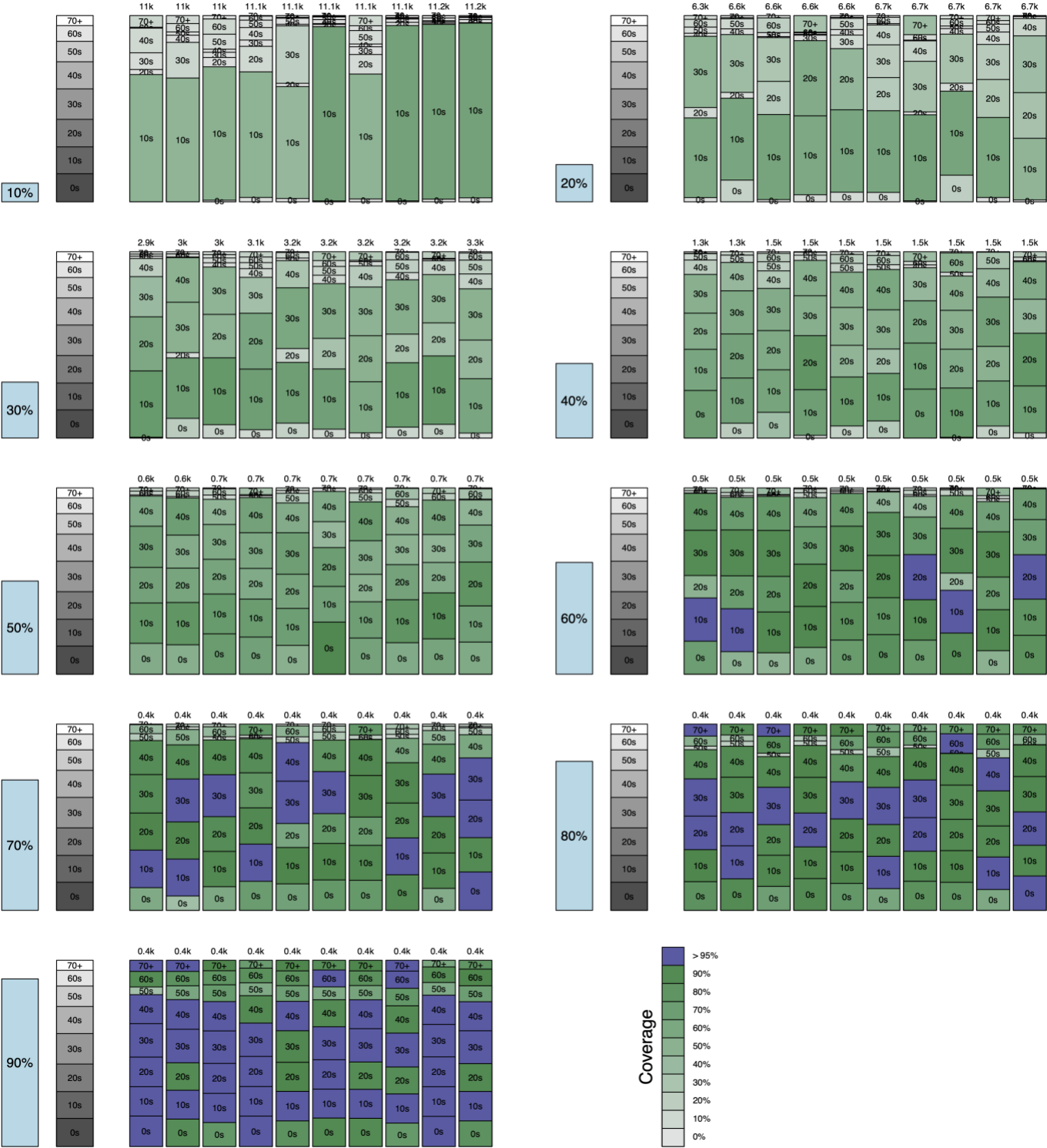


Figure S7 cont.

360-day Immune Duration



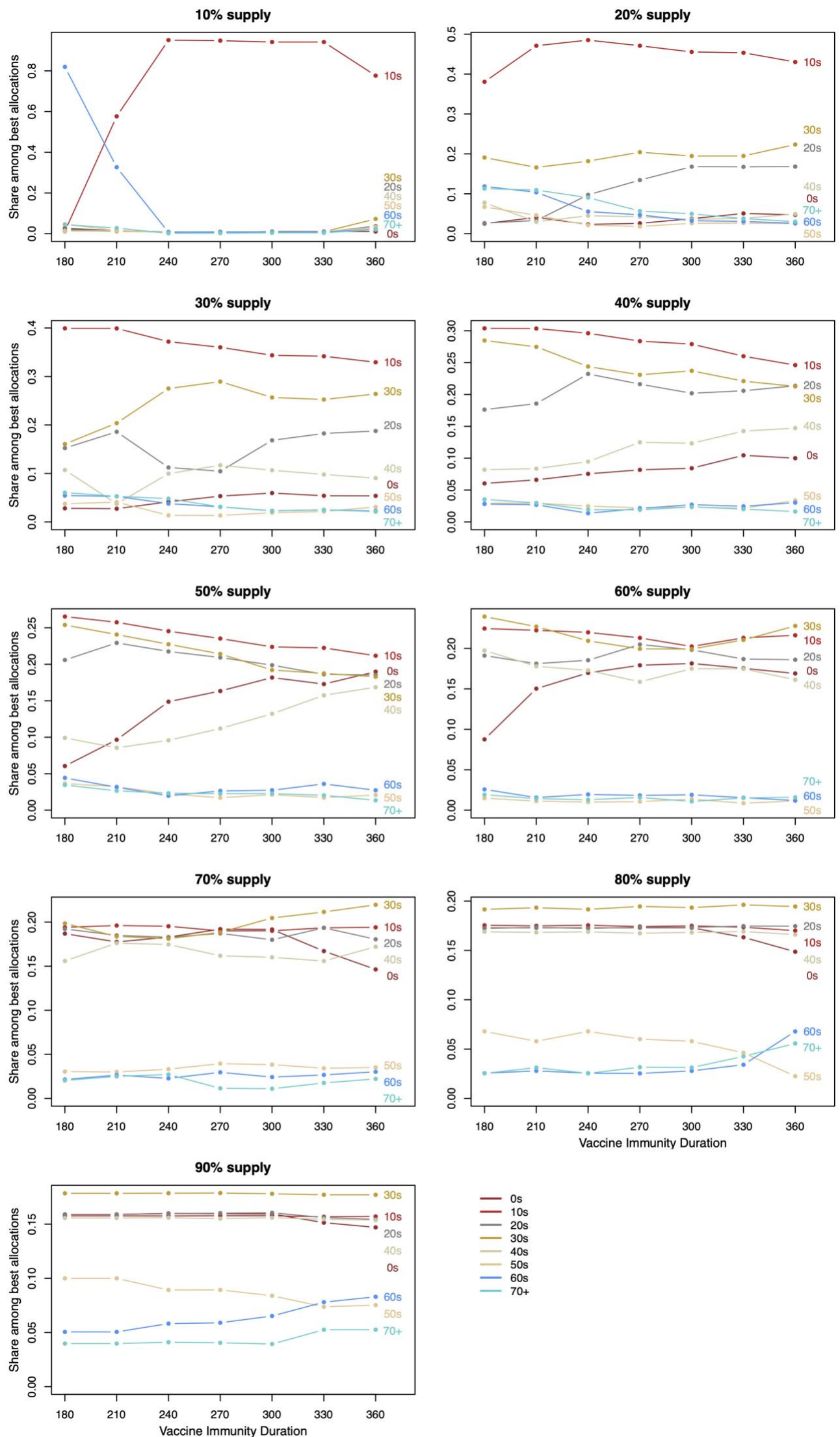


Figure S8. Shares of age groups comprising the set of ten mortality-minimizing vaccine allocations under different assumed durations of vaccine-induced immunity across vaccine supplies. The average proportion of vaccines allocated to each age group among the vaccine allocations that lead to lowest average annual mortality are shown, by vaccine supply, for each assumed duration of immunity to show how the most effective distributions of vaccines changes based on immune duration.

100% VN Population

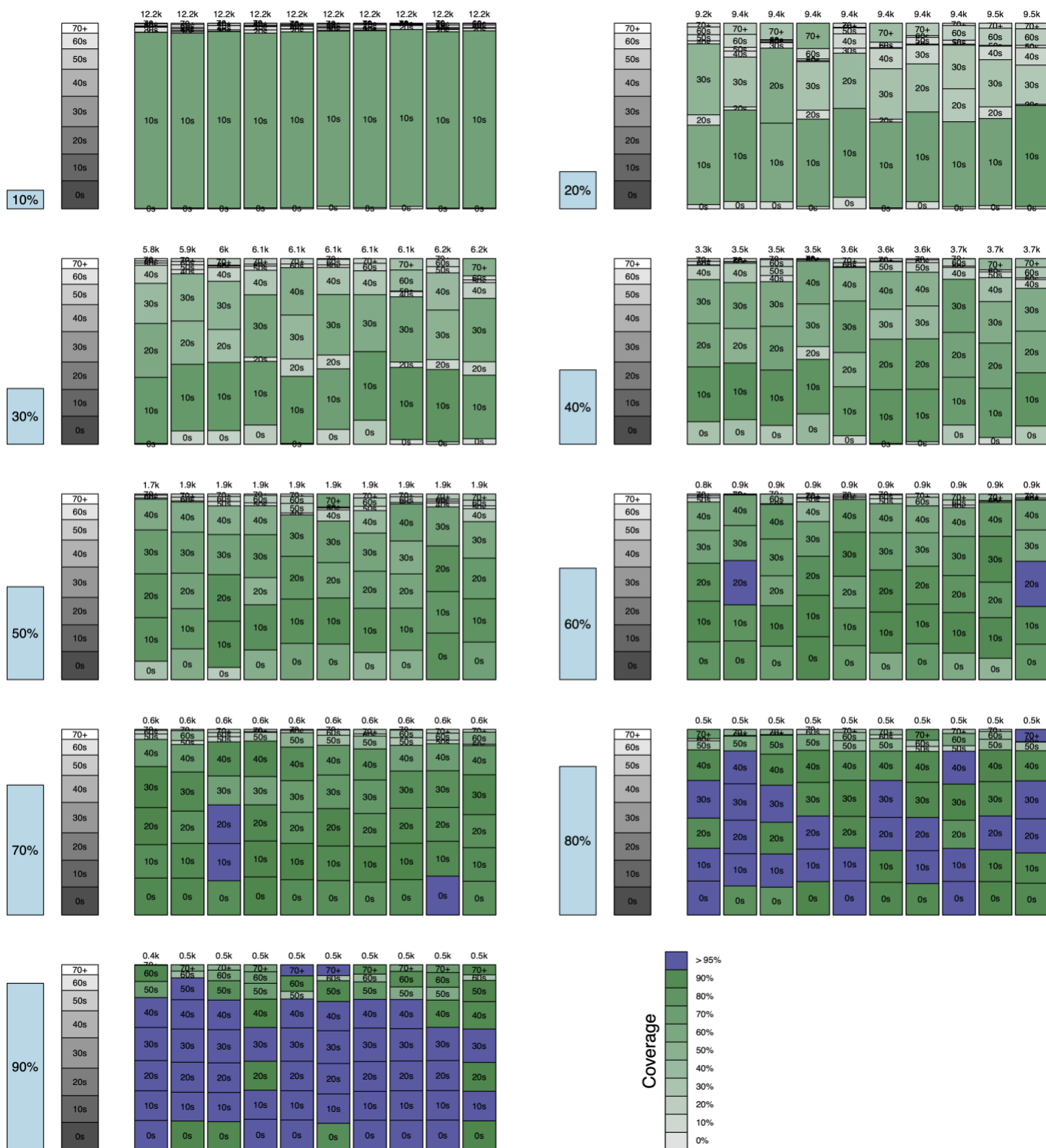


Figure S9. Optimal age-based vaccine allocations under different age compositions in a population. Mortality minimizing strategies based on vaccine supply are shown based on age compositions of Vietnam, the United States, and intermediate values. Similar to Figure 4, blue bars indicate vaccine supply relative to the population, and relative proportions of the age groups in the general population of Vietnam are compared to the proportions of vaccines allocated to age groups. The ten strategies represent those associated with the lowest average annual mortality.

Figure S9 cont.

75% VN Population, 25% US Population

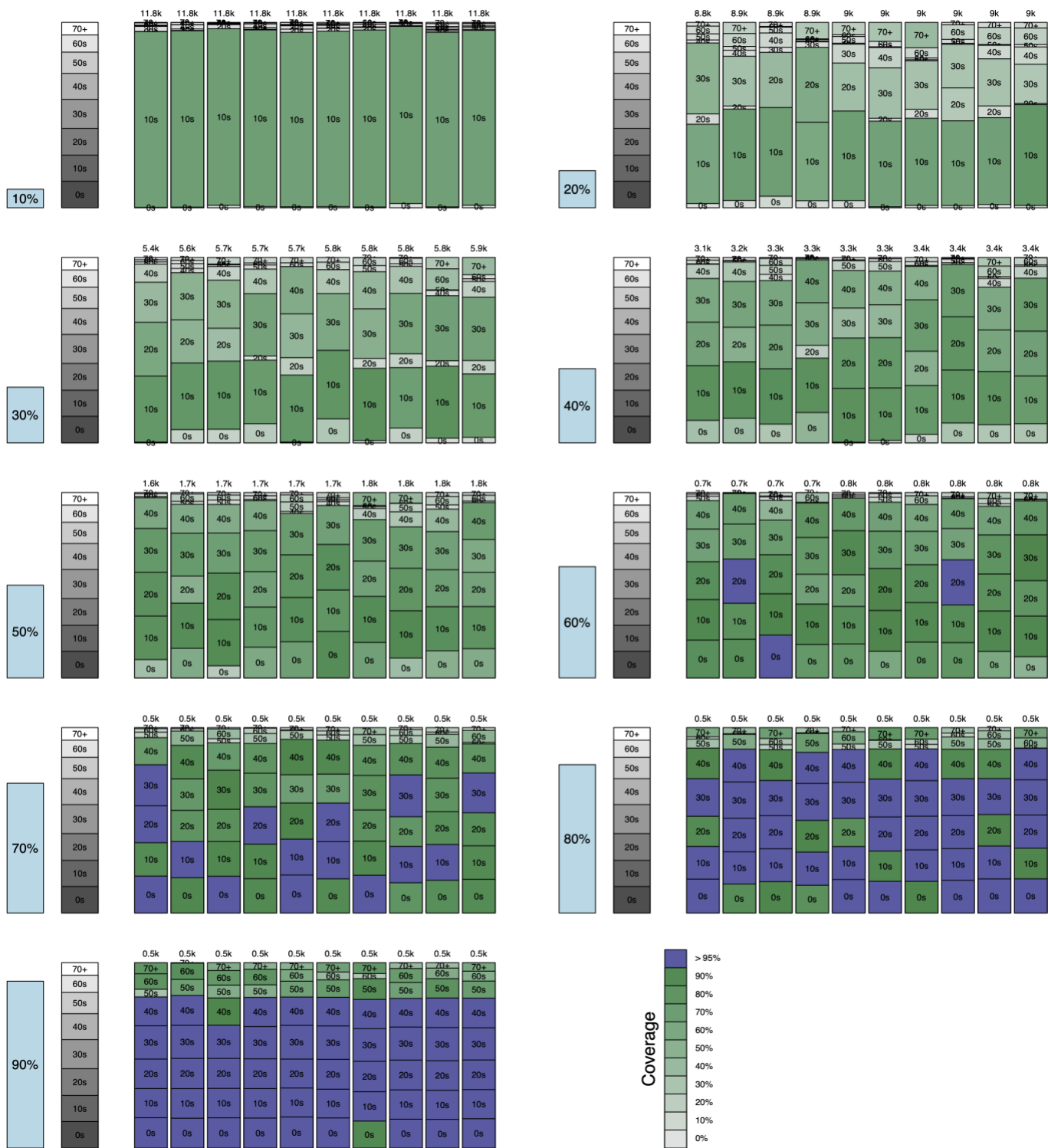


Figure S9 cont.

50% VN Population, 50% US Population

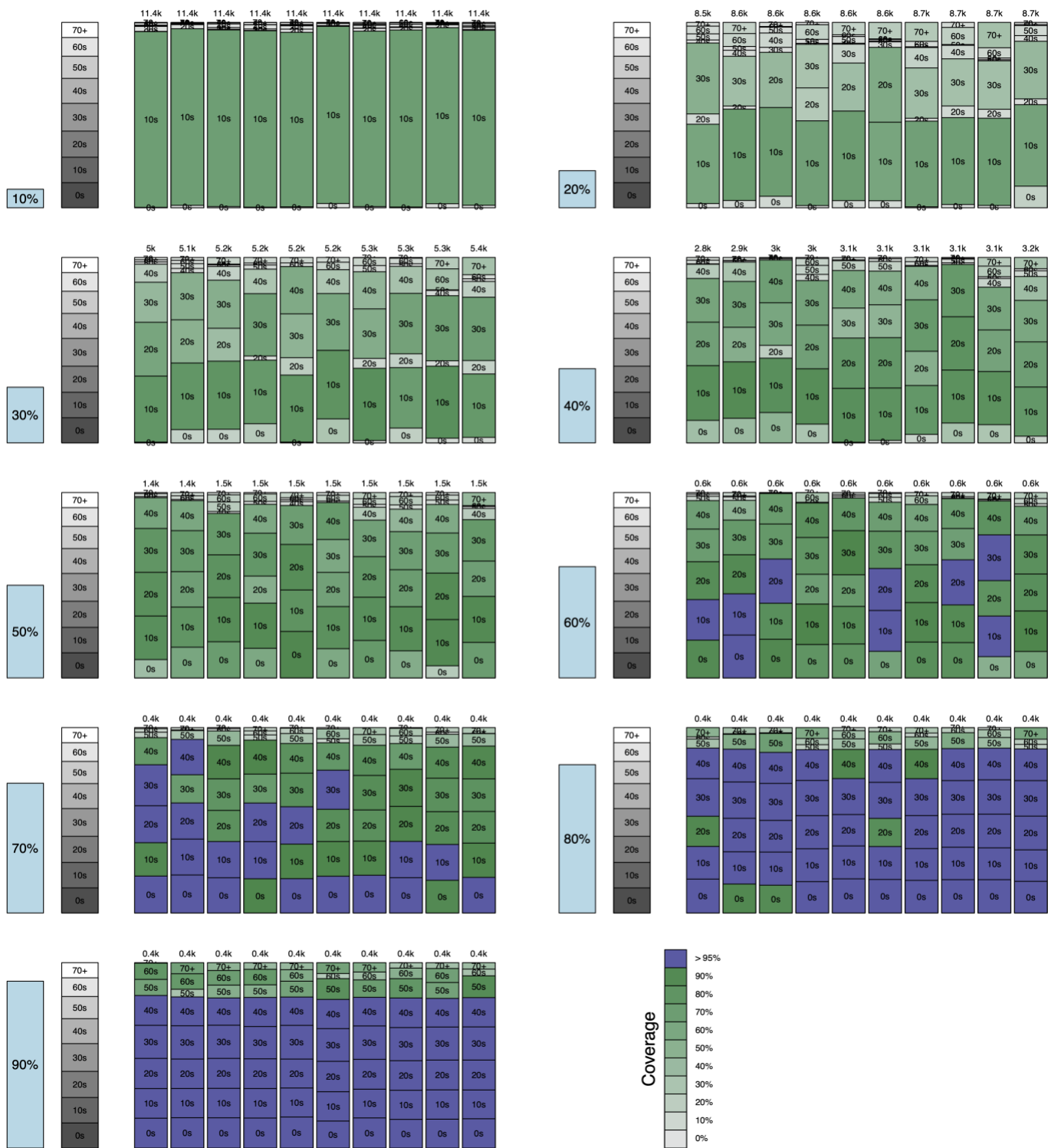


Figure S9 cont.

25% VN Population, 75% US Population

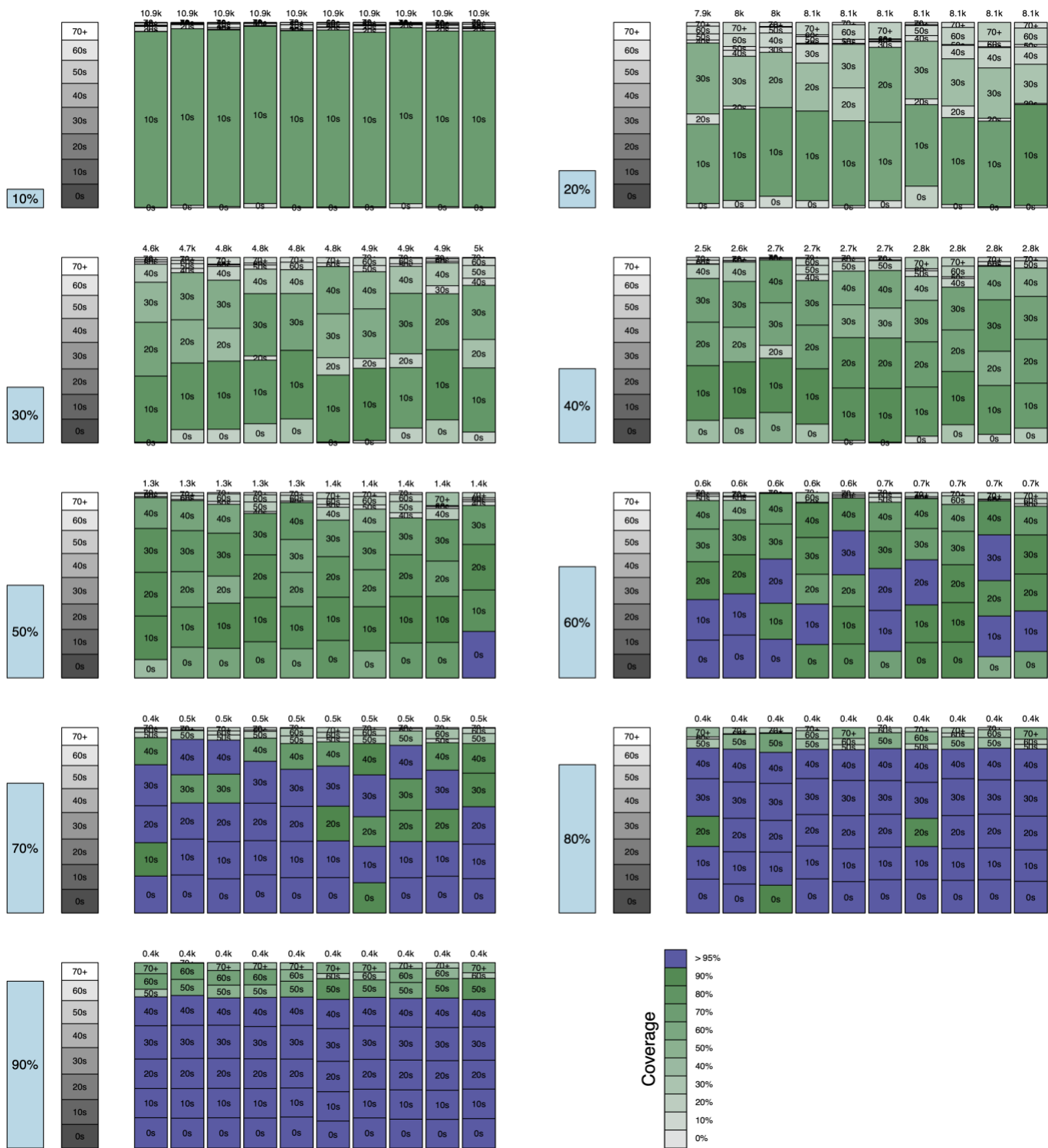
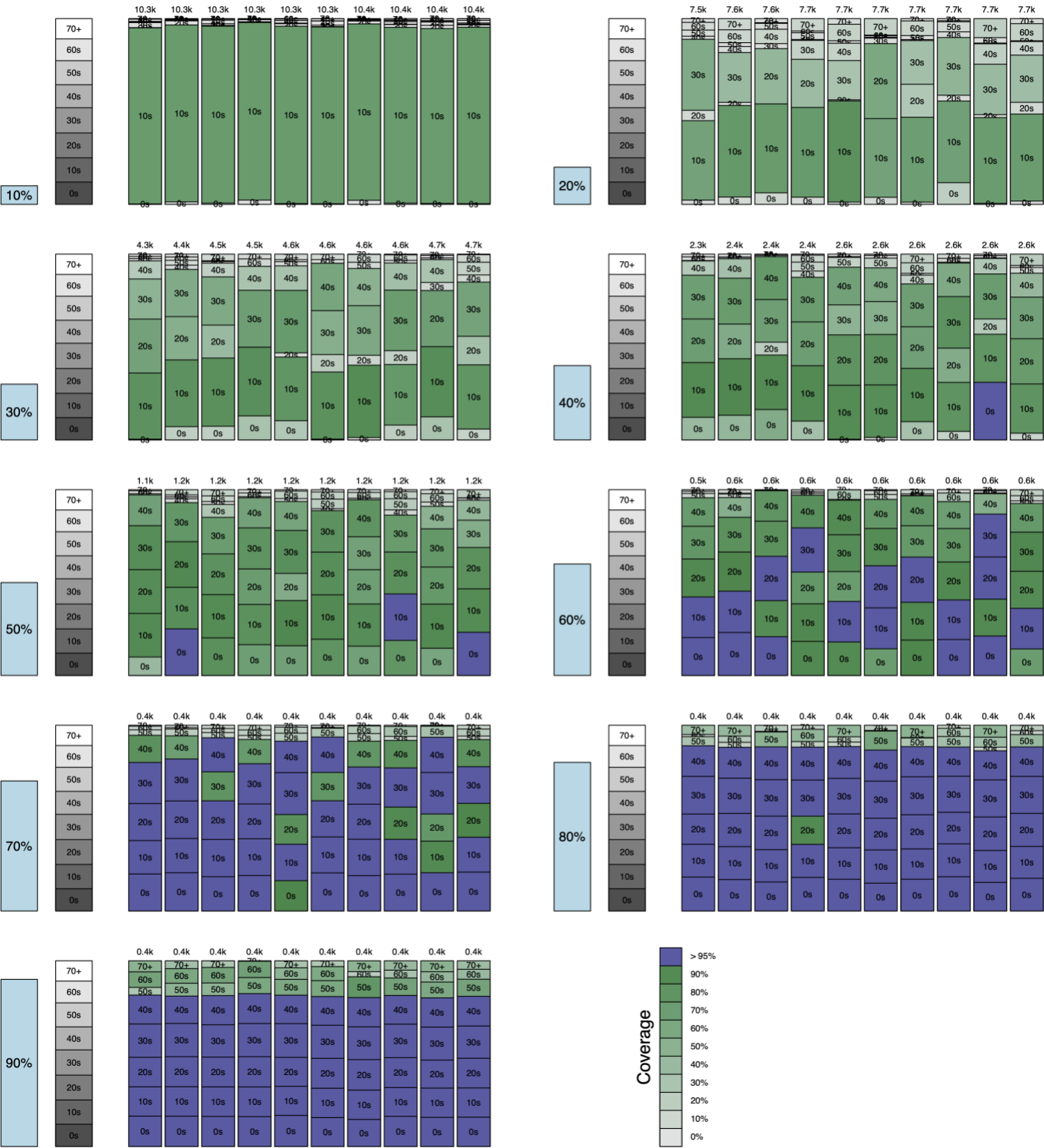


Figure S9 cont.

100% US Population



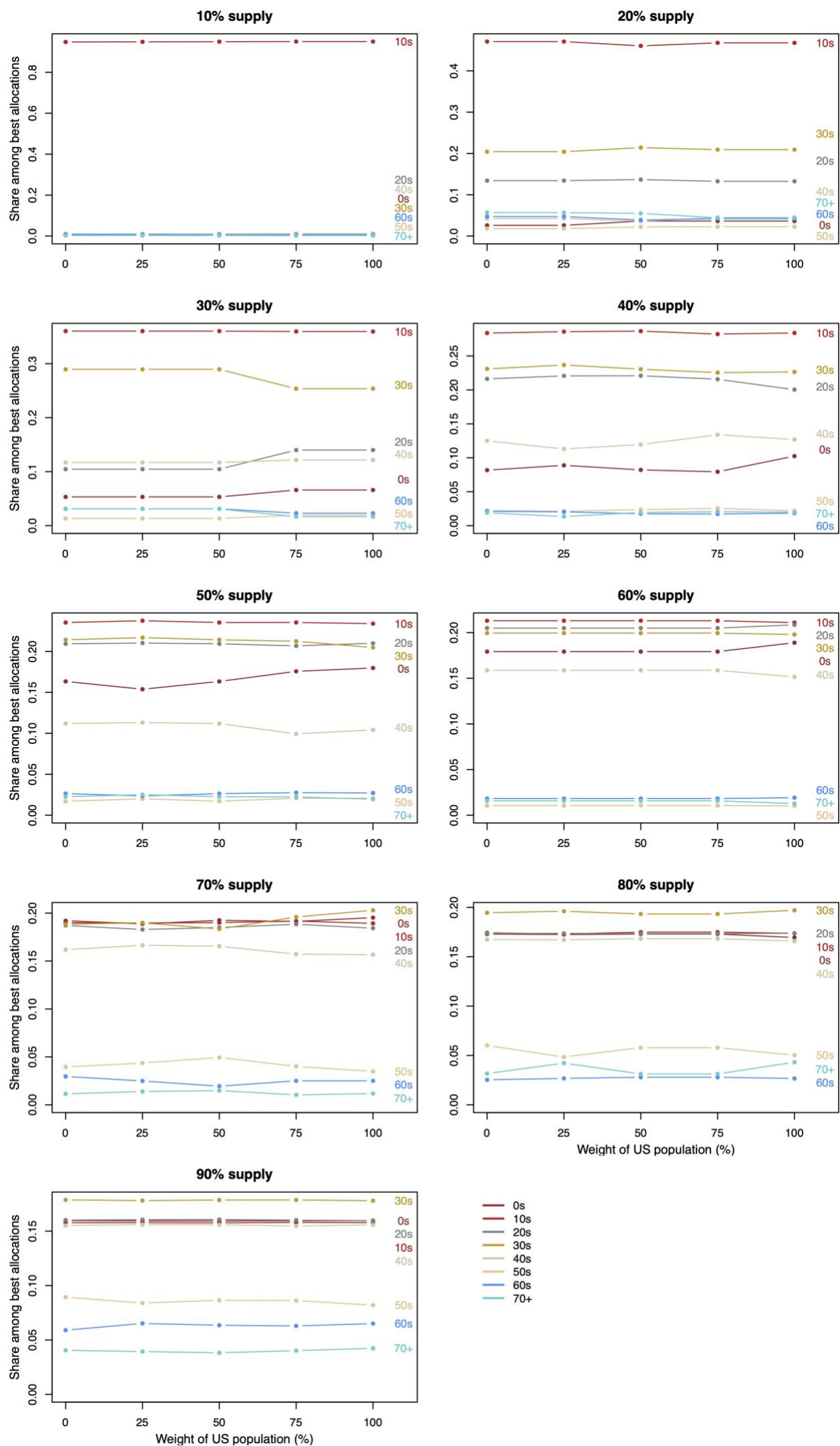
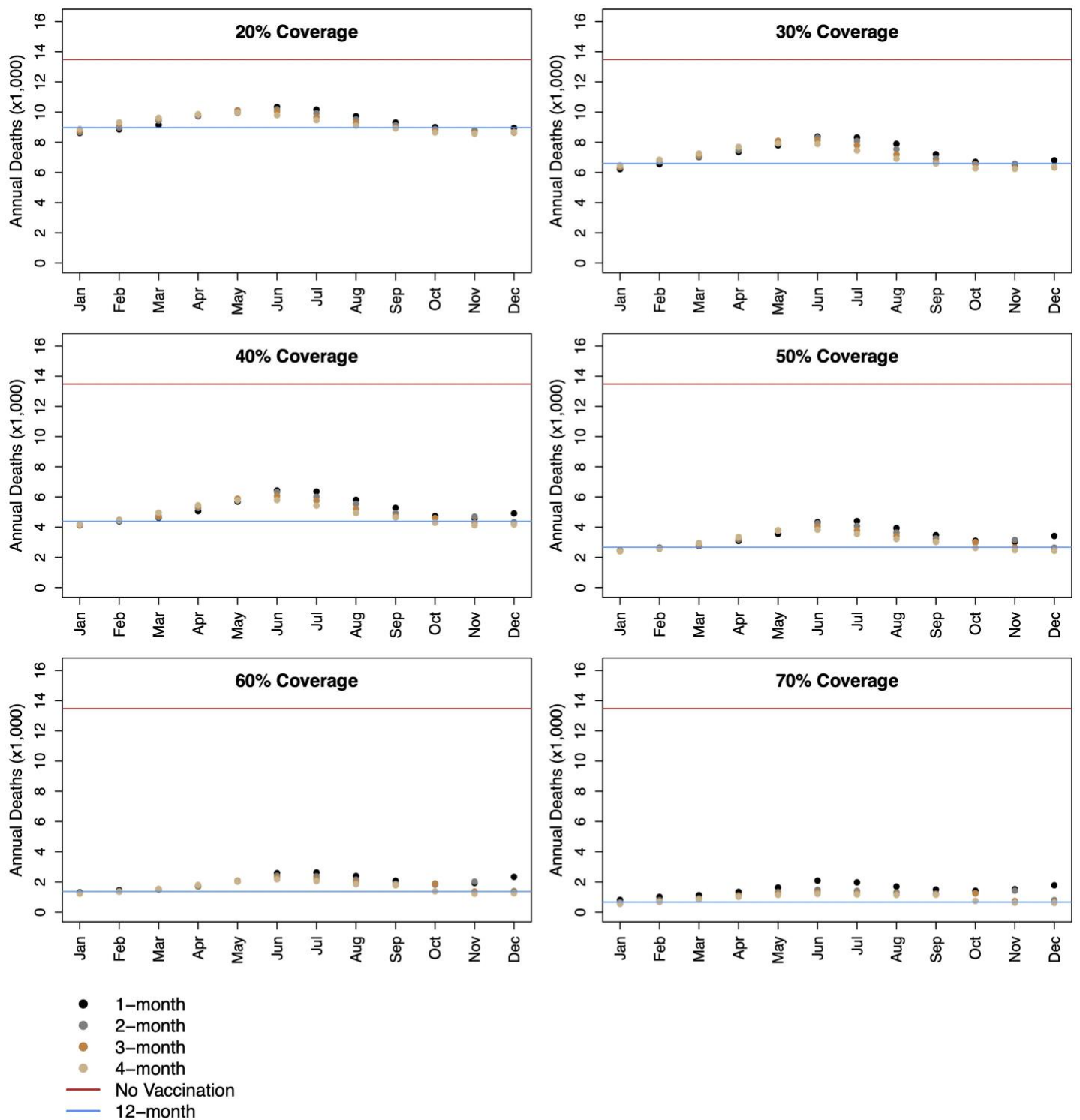


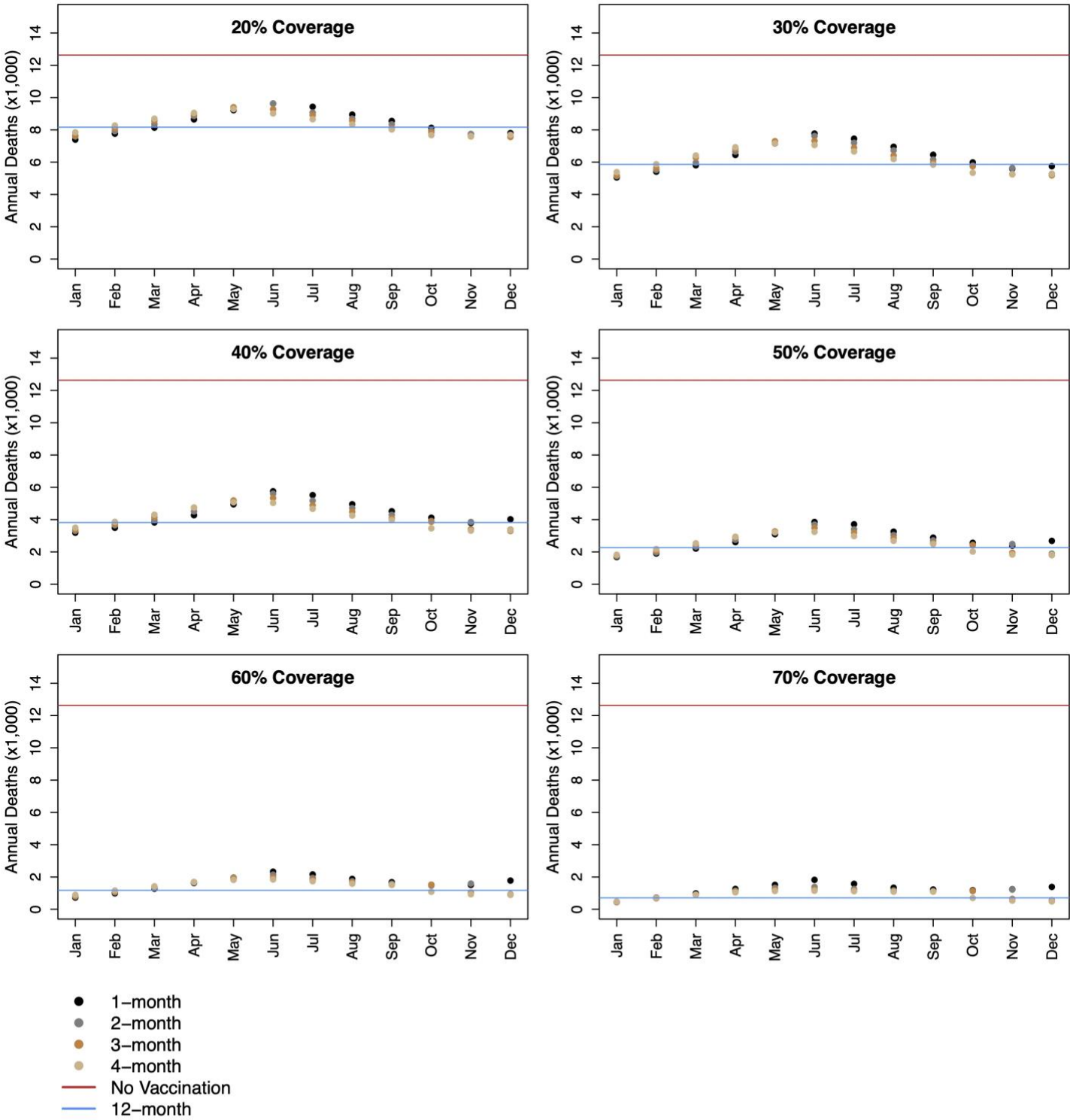
Figure S10. Shares of age groups comprising the set of ten mortality-minimizing vaccine allocations under different population age structures across vaccine supplies. The average proportion of vaccines allocated to each age group among the vaccine allocations that lead to lowest average annual mortality are shown, by age structure on a gradient between the age structures of Vietnam and the United States, for each assumed duration of immunity to show how the most effective distributions of vaccines changes based on the age demographics of the population.



Off school term, 25% reduction in contact

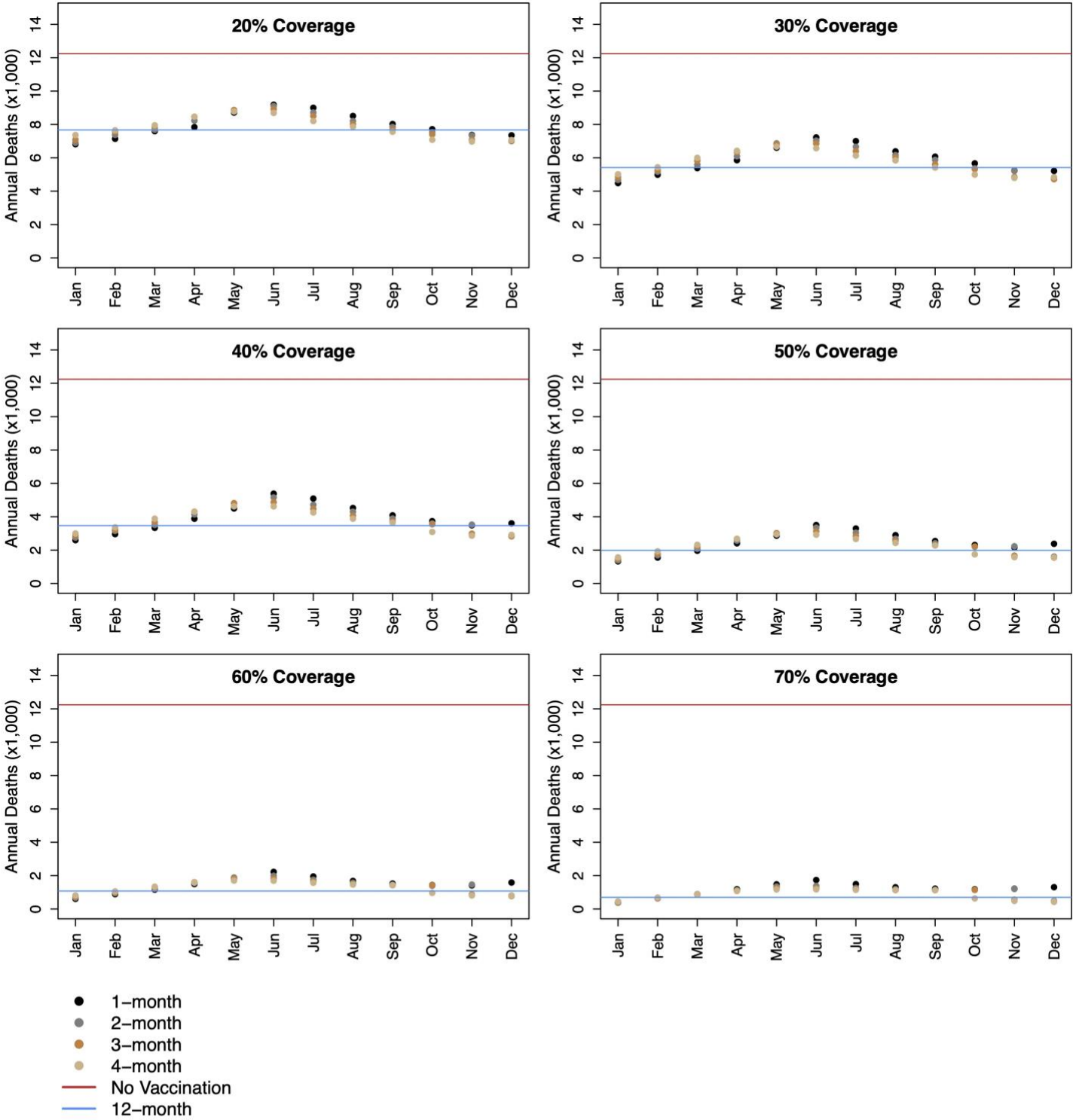
Figure S11. Results from selecting optimal timing of vaccines under time-varying contact matrices. Results of vaccine timing are shown based on contact patterns decreasing among children outside of the school year, decreasing among the full population in summer, and increasing among the full population for the Lunar New Year holiday. Similar to Figure S2, each panel shows the average annual mortality at a given vaccine coverage when beginning vaccination at the specified month and administering vaccines over a span of one to four months. Blue lines indicate average mortality when vaccinating continuously over 12 months. Under each start month and duration, population coverage over the calendar year is equal.

Figure S11 cont.



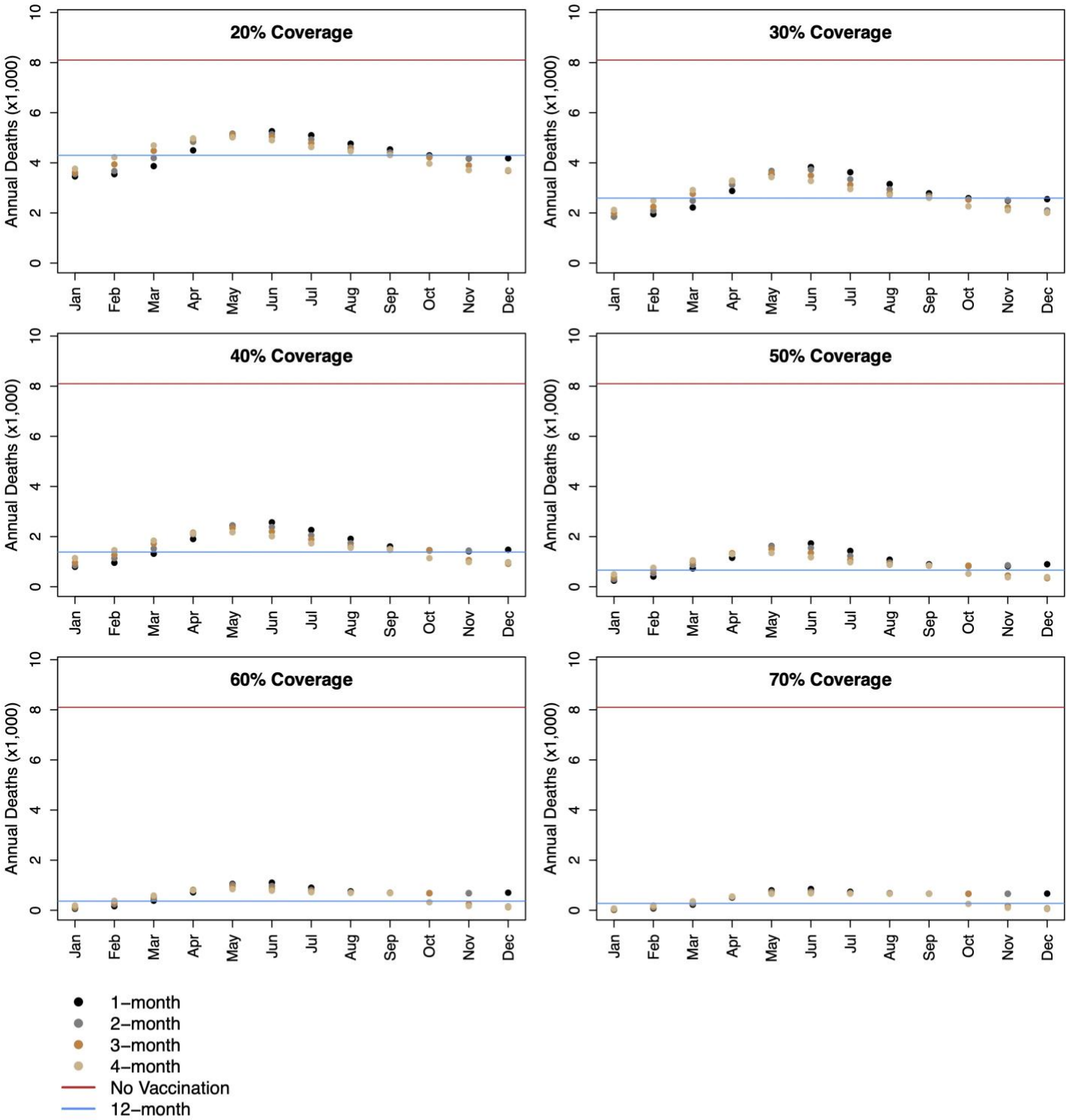
Off school term, 50% reduction in contact

Figure S11 cont.



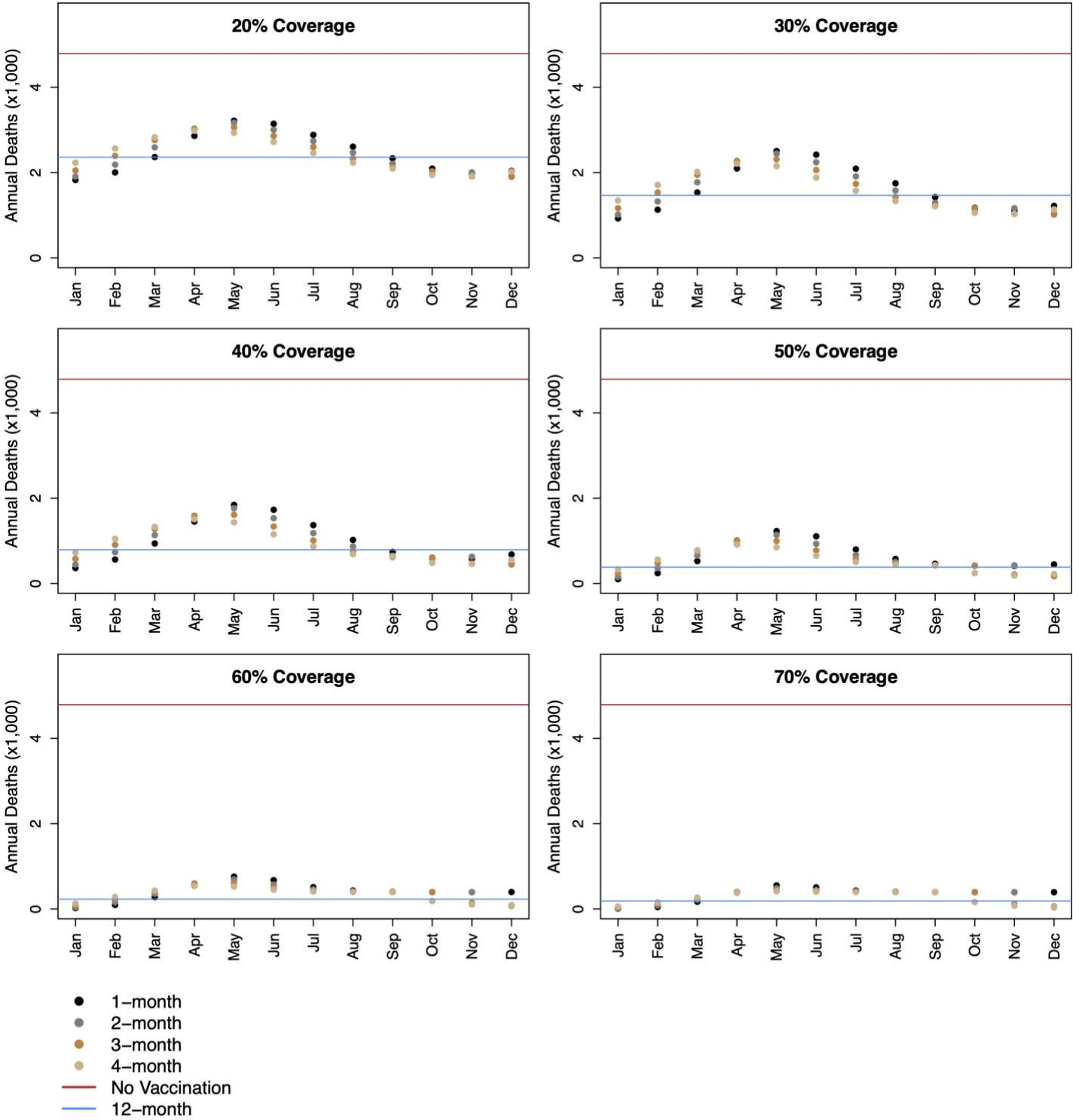
Off school term, 75% reduction in contact

Figure S11 cont.



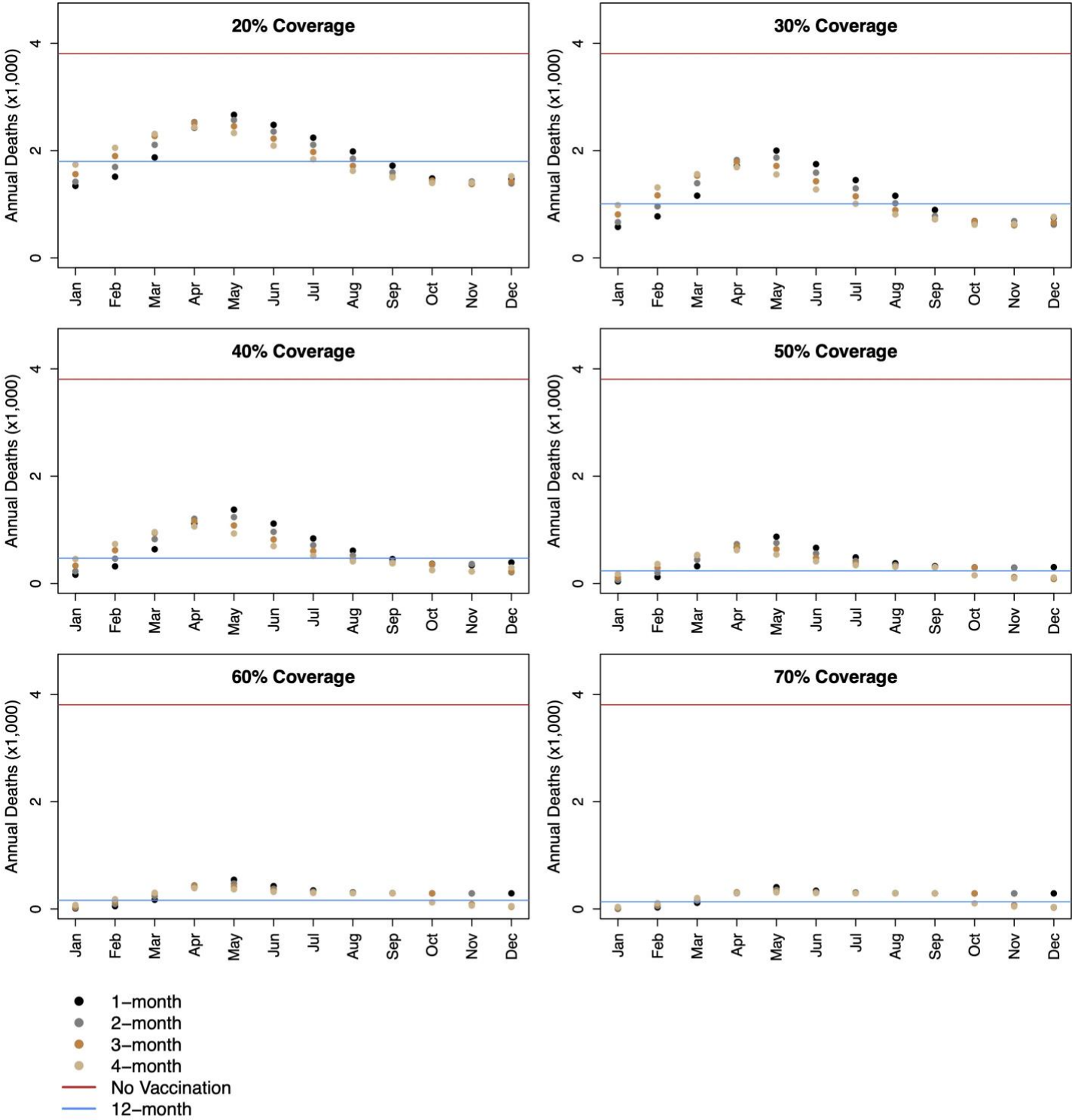
Summer season, 25% reduction in contact

Figure S11 cont.



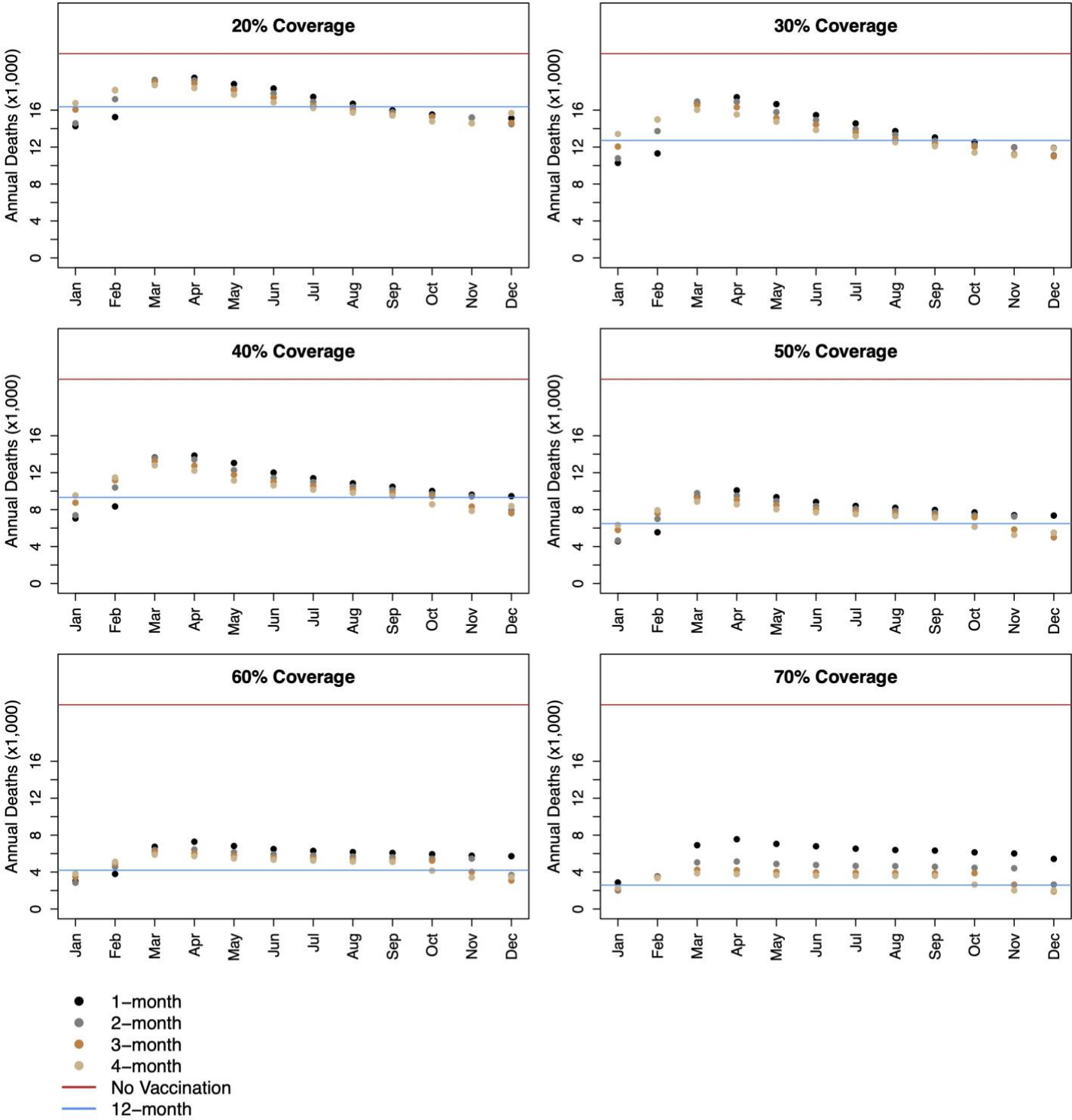
Summer season, 50% reduction in contact

Figure S11 cont.



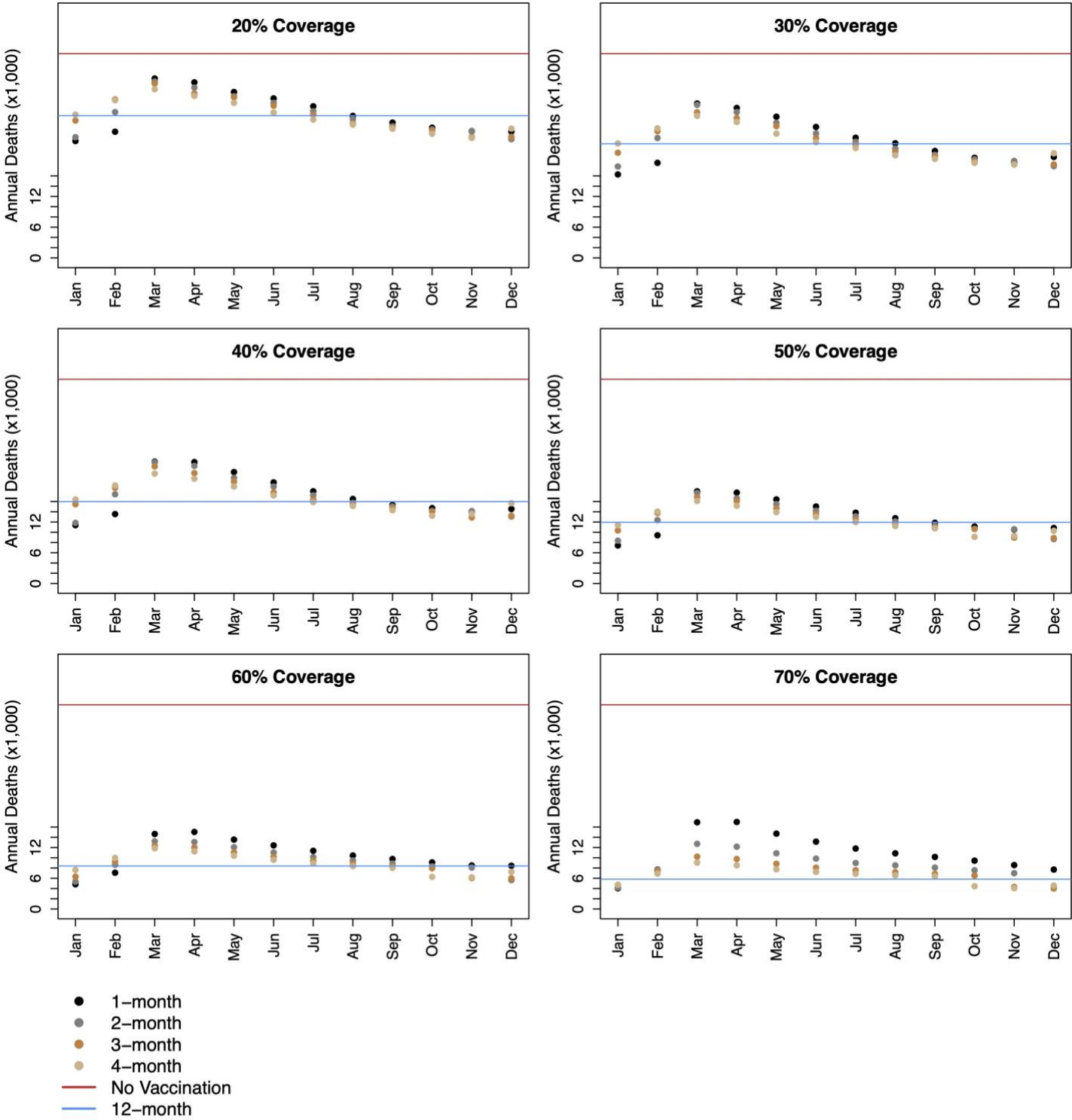
Summer season, 75% reduction in contact

Figure S11 cont.



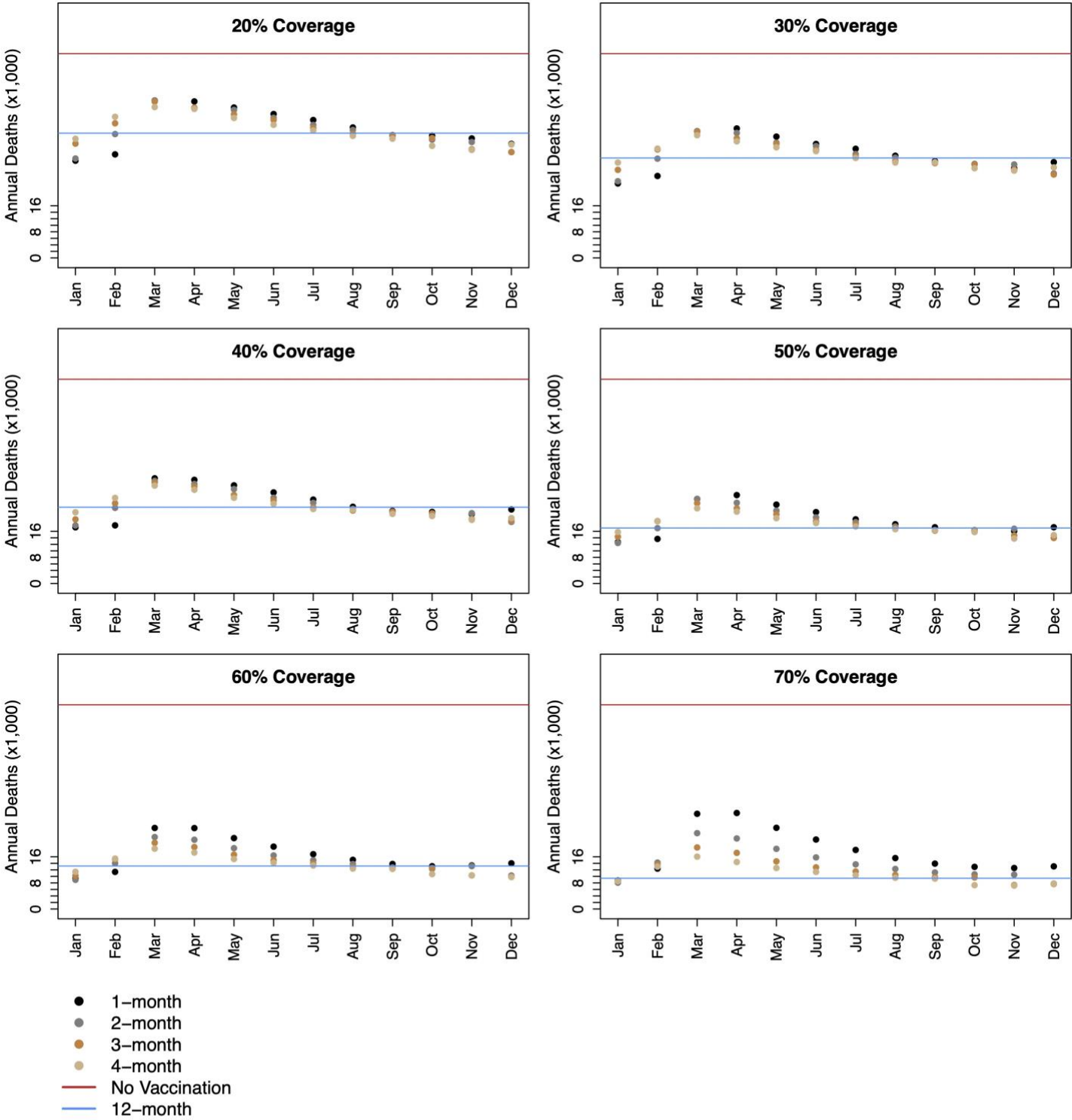
Annual holiday, 25% increase in contact

Figure S11 cont.



Annual holiday, 50% increase in contact

Figure S11 cont.



Annual holiday, 75% increase in contact

Off school term, 25% reduction in contact

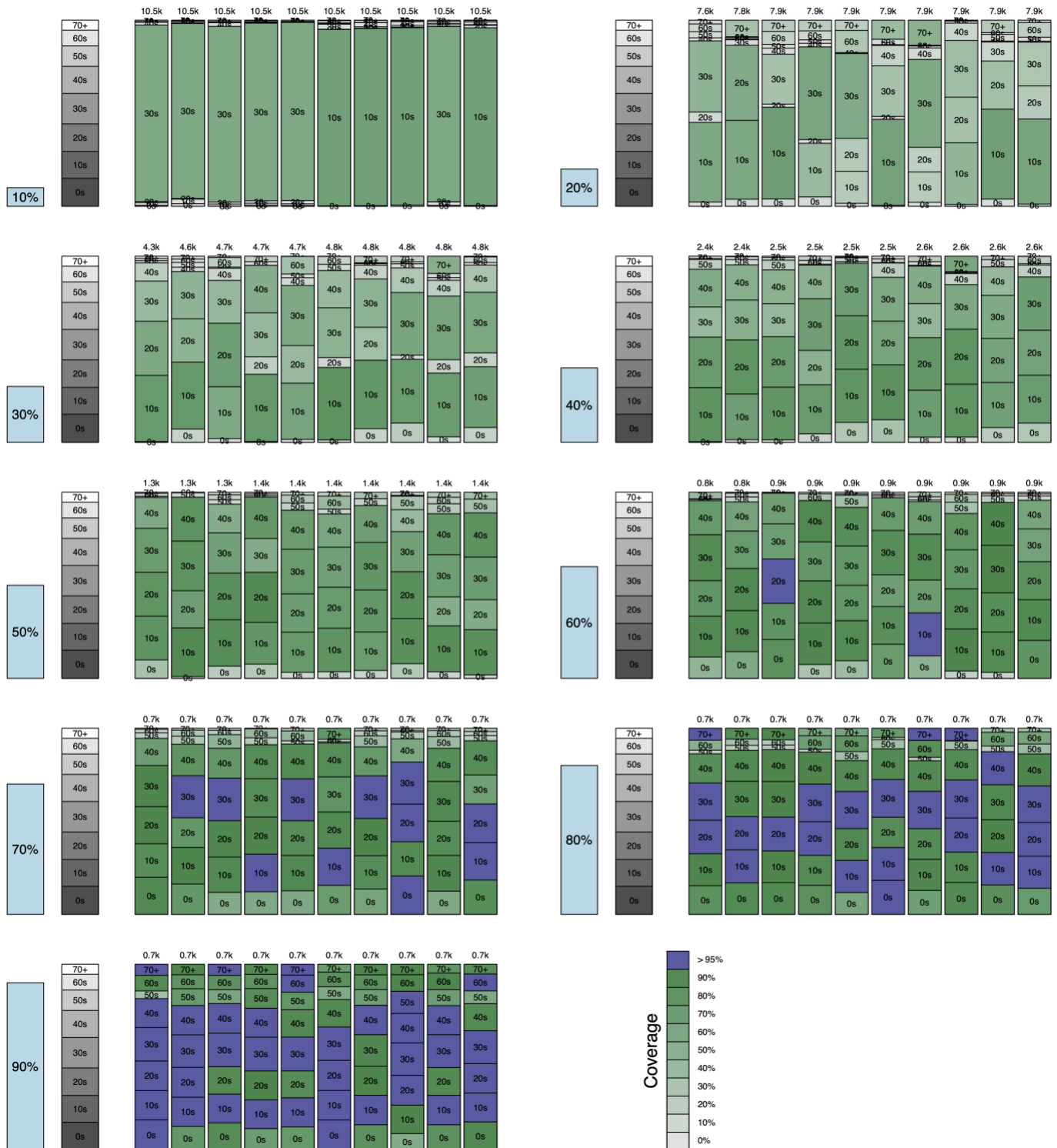


Figure S12. Optimal age-based vaccine allocations under different assumed time-varying contact matrices. Mortality minimizing strategies are shown based on contact patterns decreasing among children outside of the school year, decreasing among the full population in summer, and increasing among the full population for the Lunar New Year holiday. Similar to Figure 4, blue bars indicate vaccine supply relative to the population, and relative proportions of the age groups in the general population of Vietnam are compared to the proportions of vaccines allocated to age groups. The ten strategies shown represent those associated with the lowest average annual mortality.

Figure S12 cont.

Off school term, 50% reduction in contact

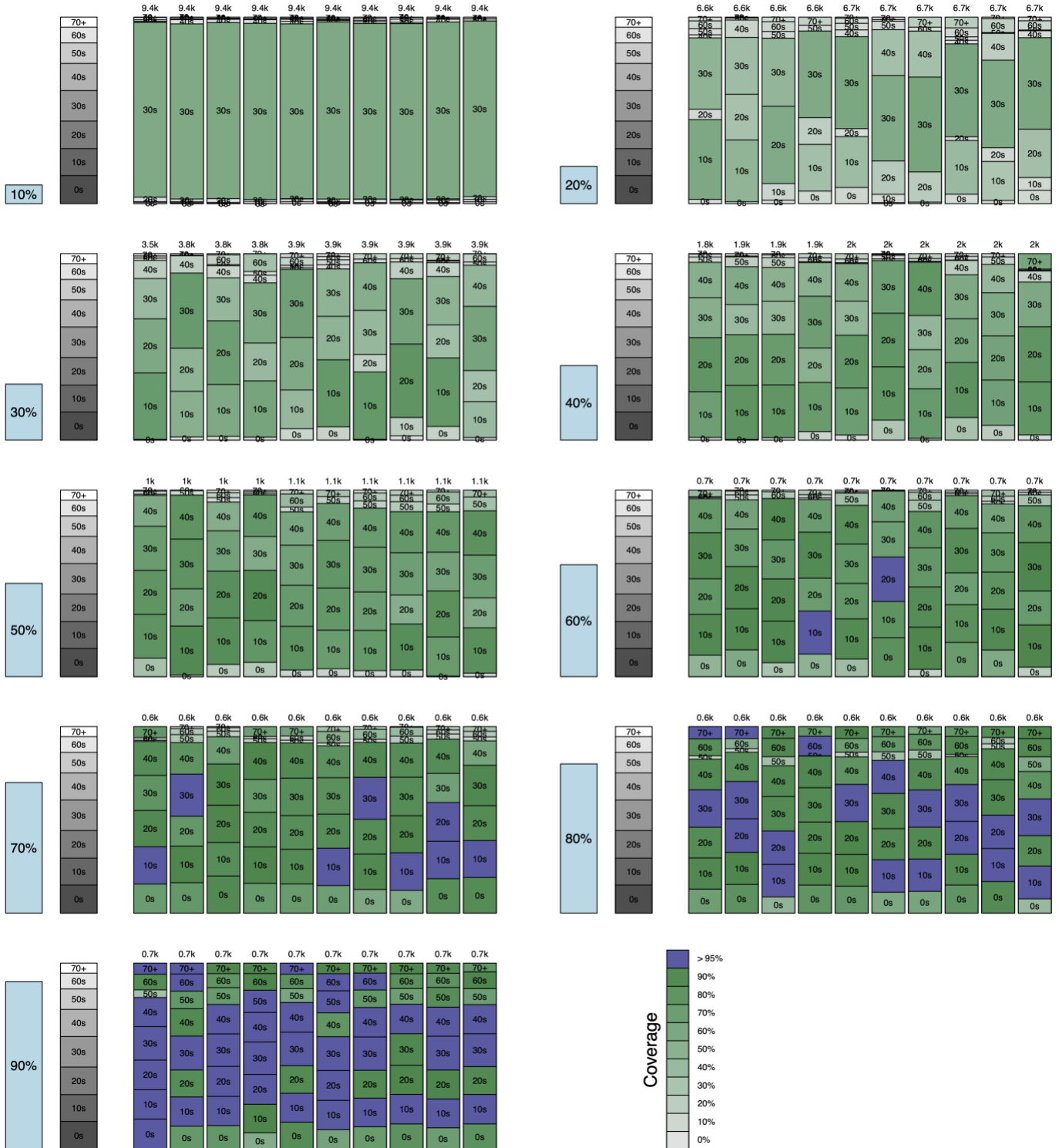


Figure S12 cont.

Off school term, 75% reduction in contact

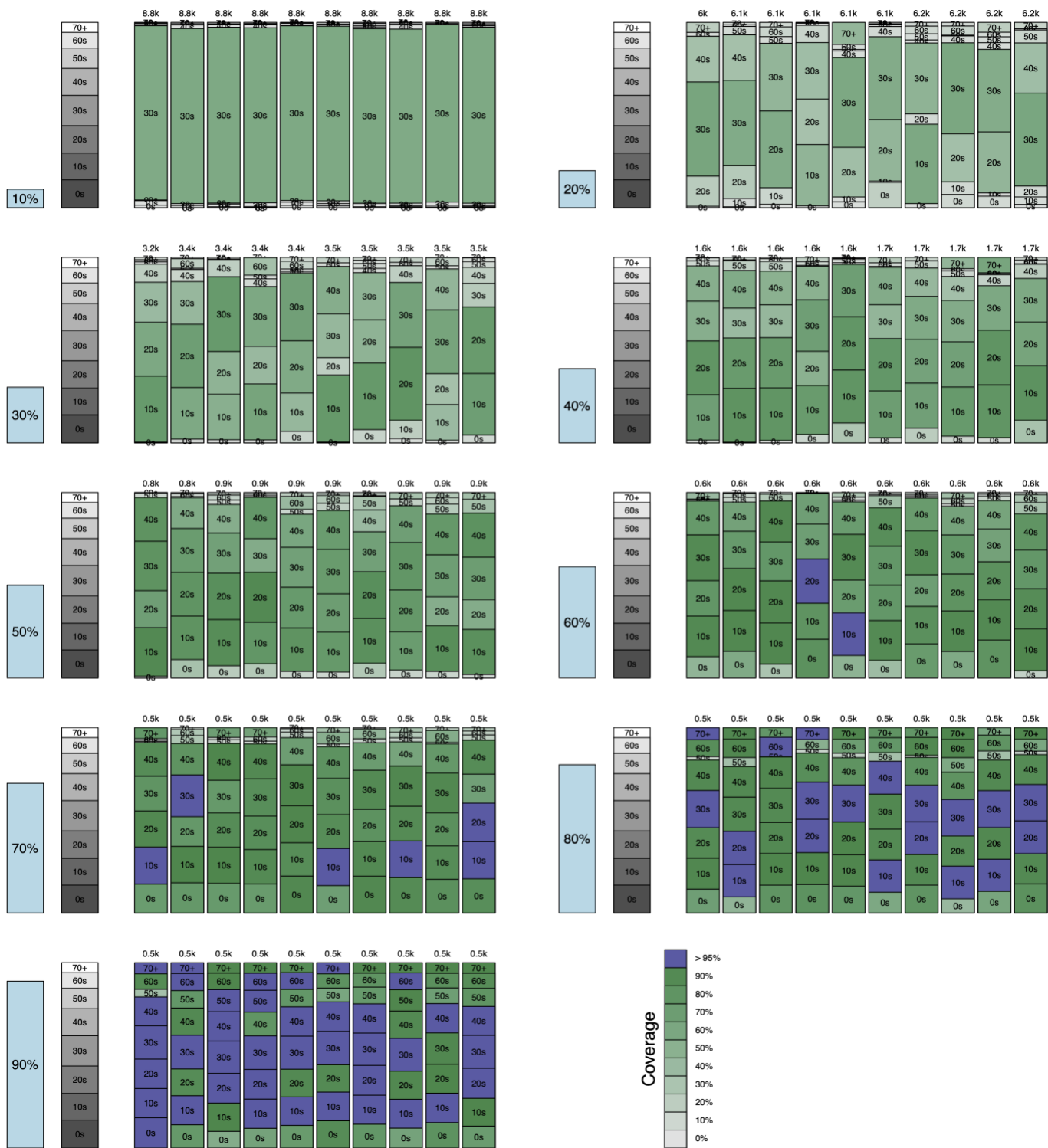


Figure S12 cont.

Summer season, 25% reduction in contact

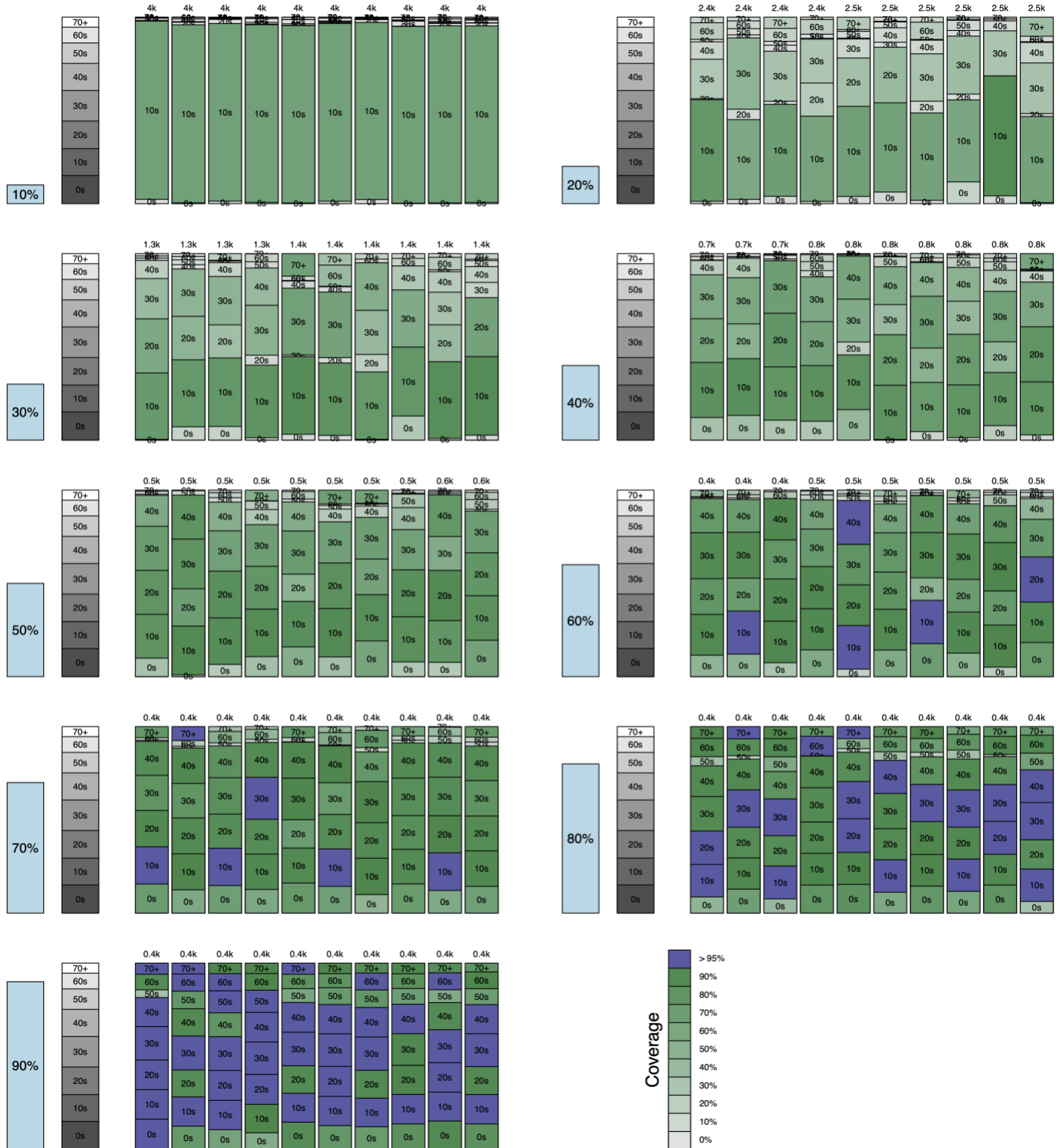


Figure S12 cont.

Summer season, 50% reduction in contact

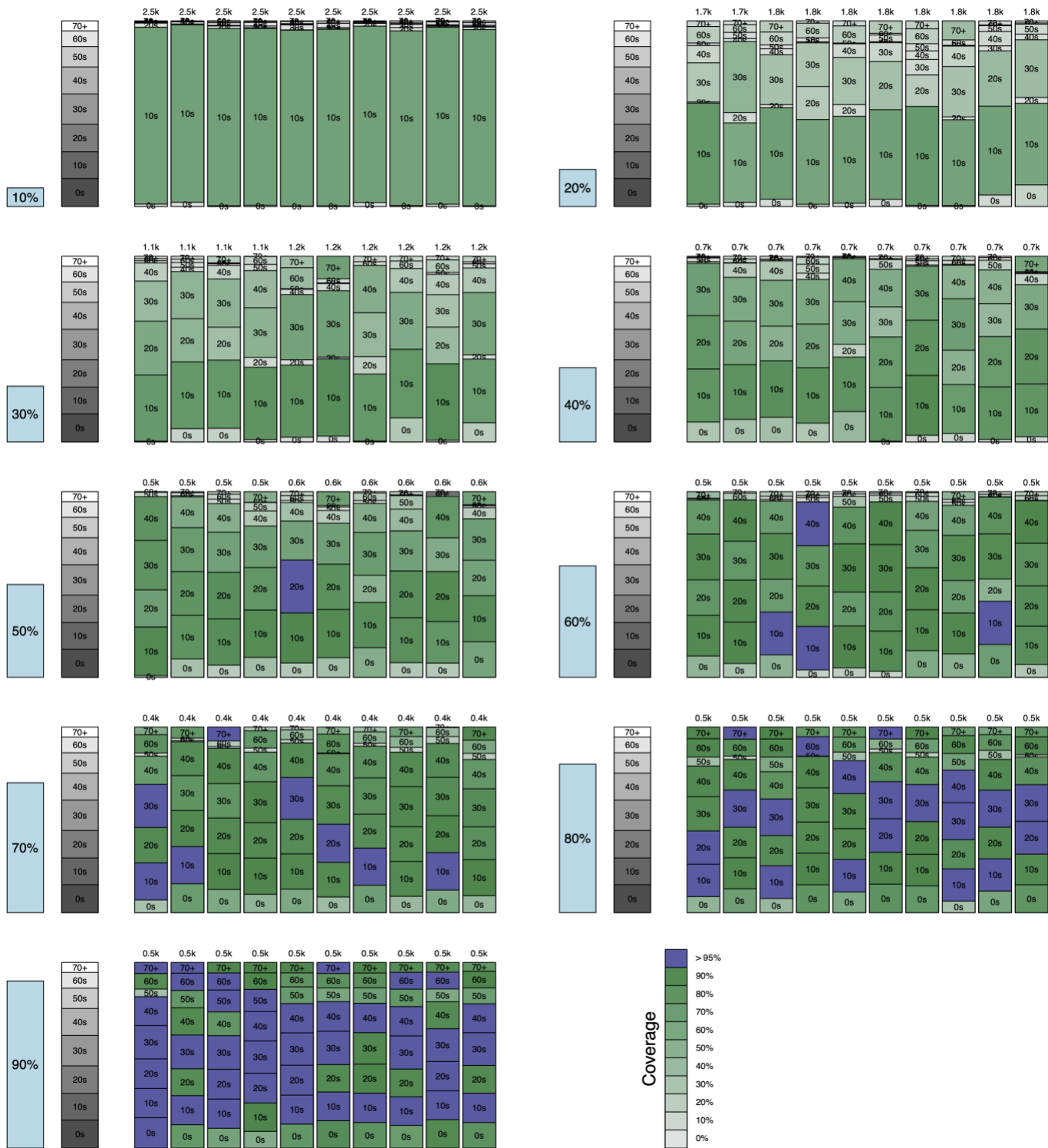


Figure S12 cont.

Summer season, 75% reduction in contact

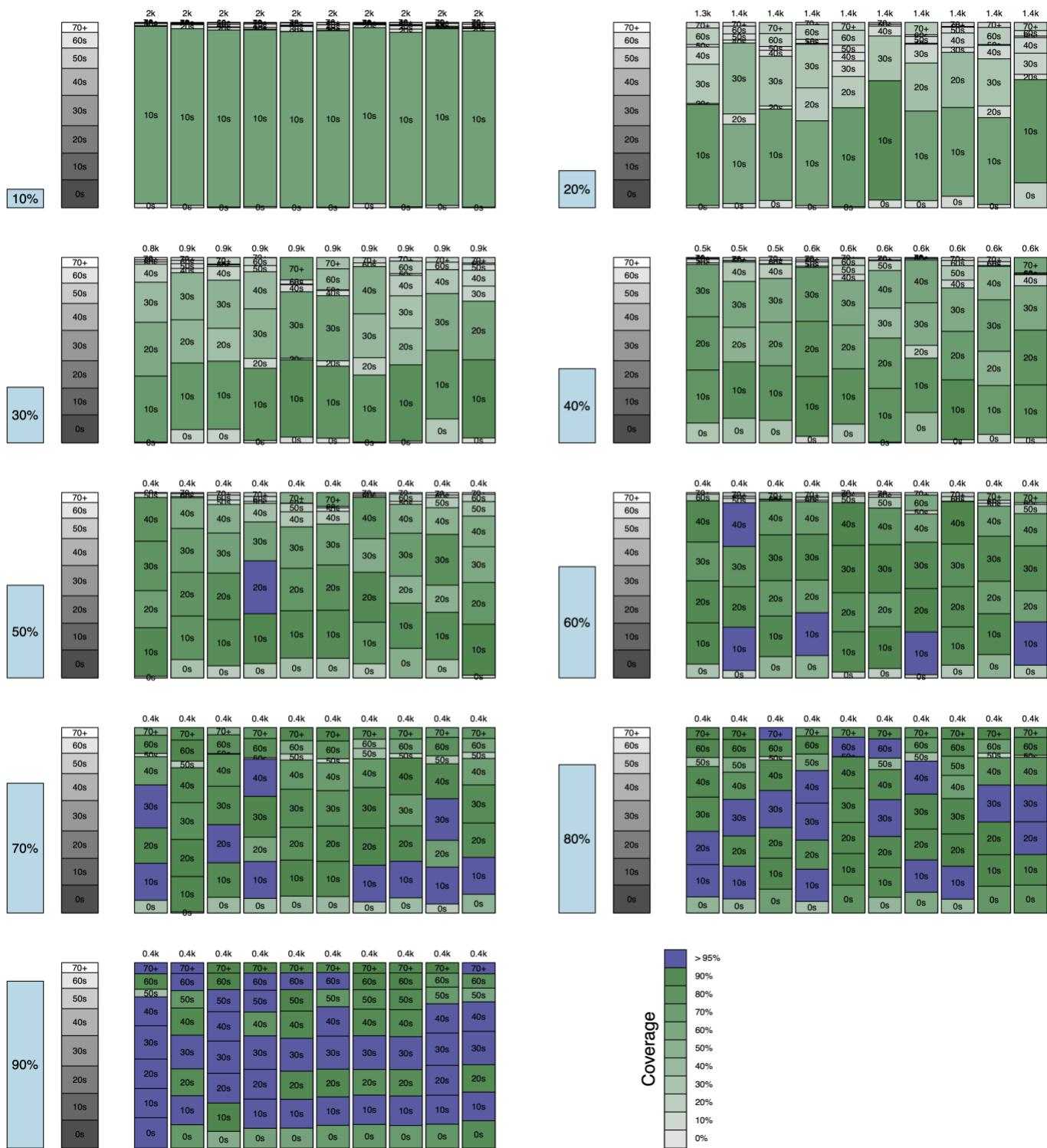


Figure S12 cont.

Annual holiday, 25% increase in contact

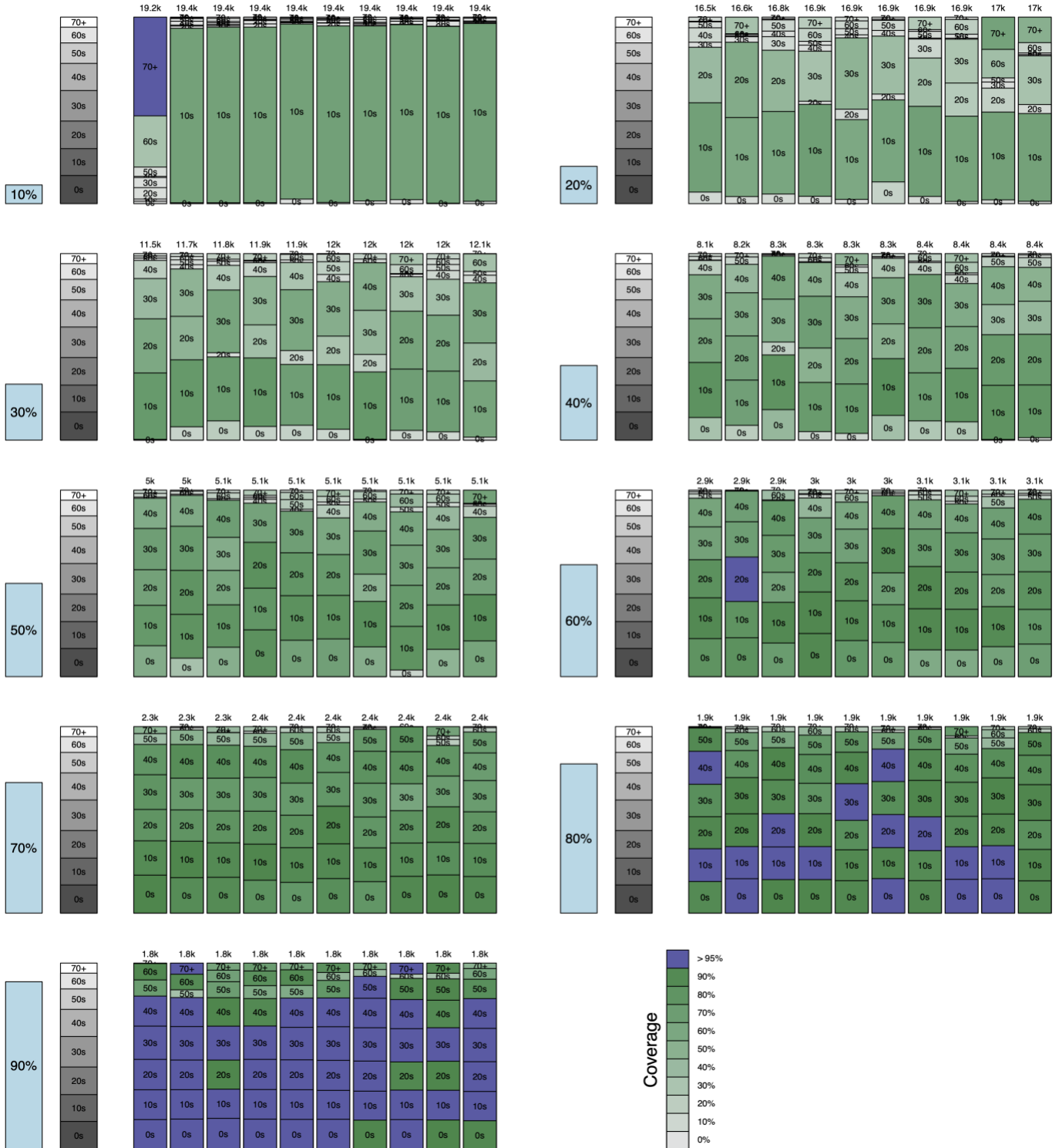


Figure S12 cont.

Annual holiday, 50% increase in contact

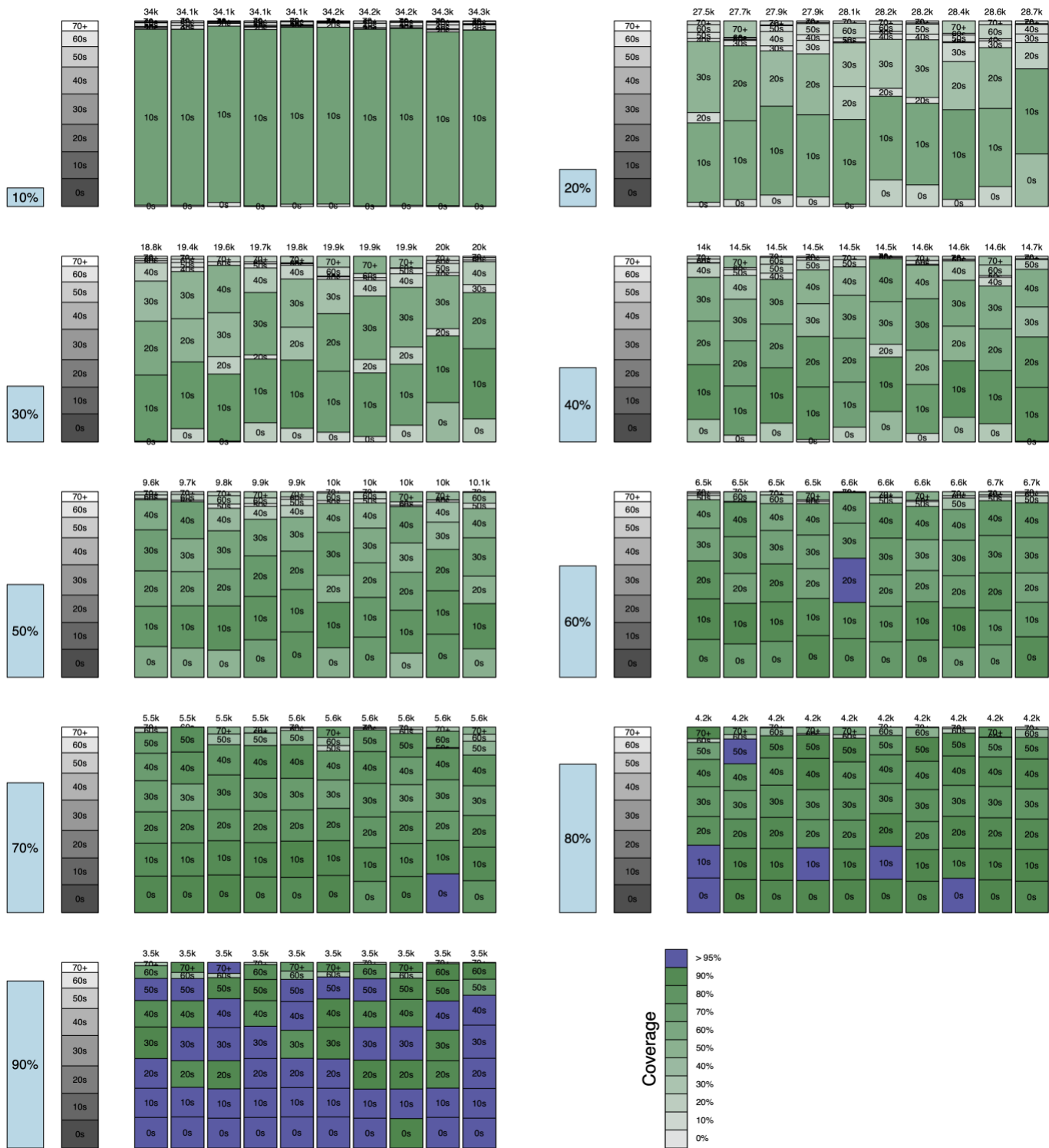
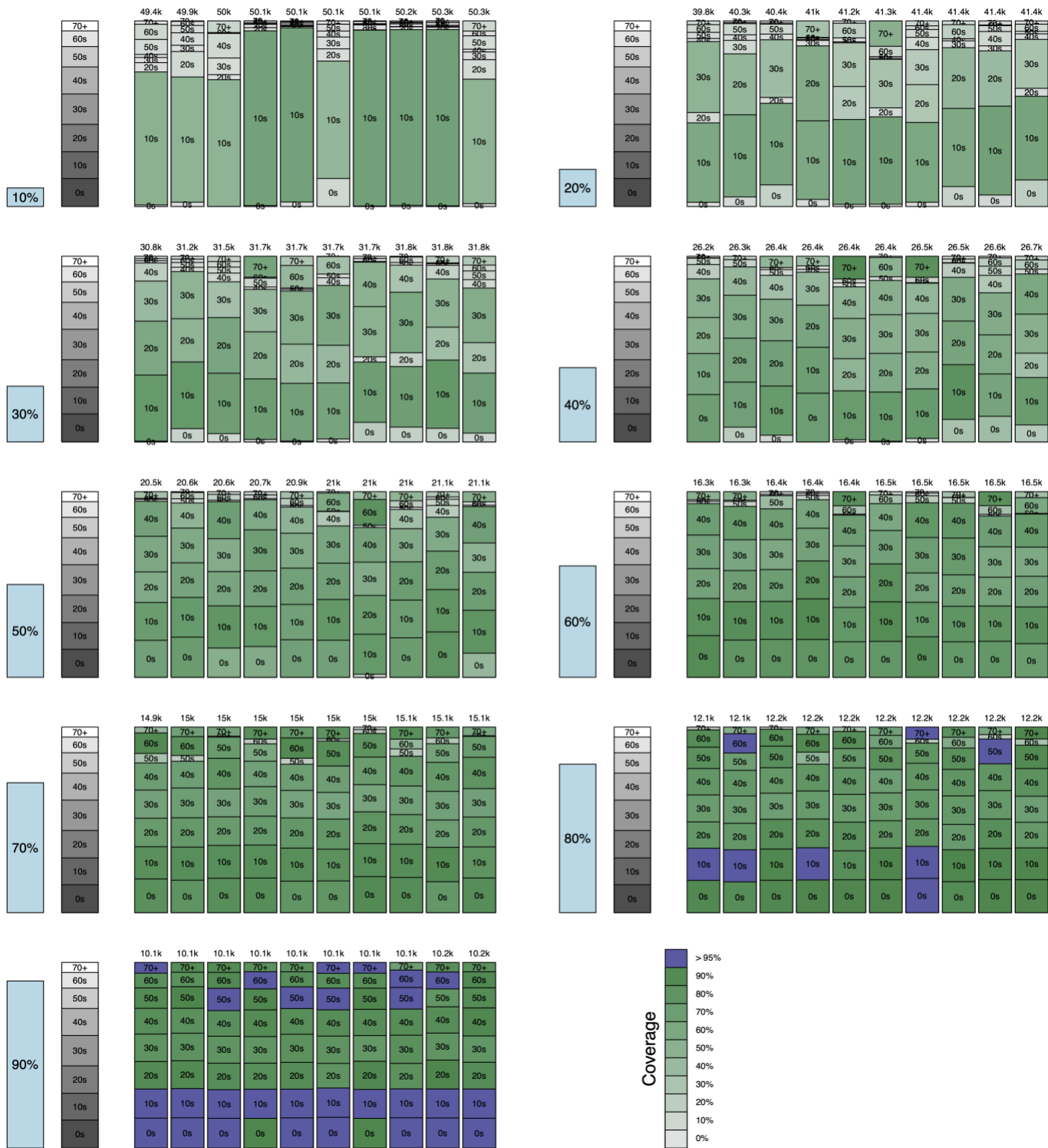


Figure S12 cont.

Annual holiday, 75% increase in contact



10% Supply

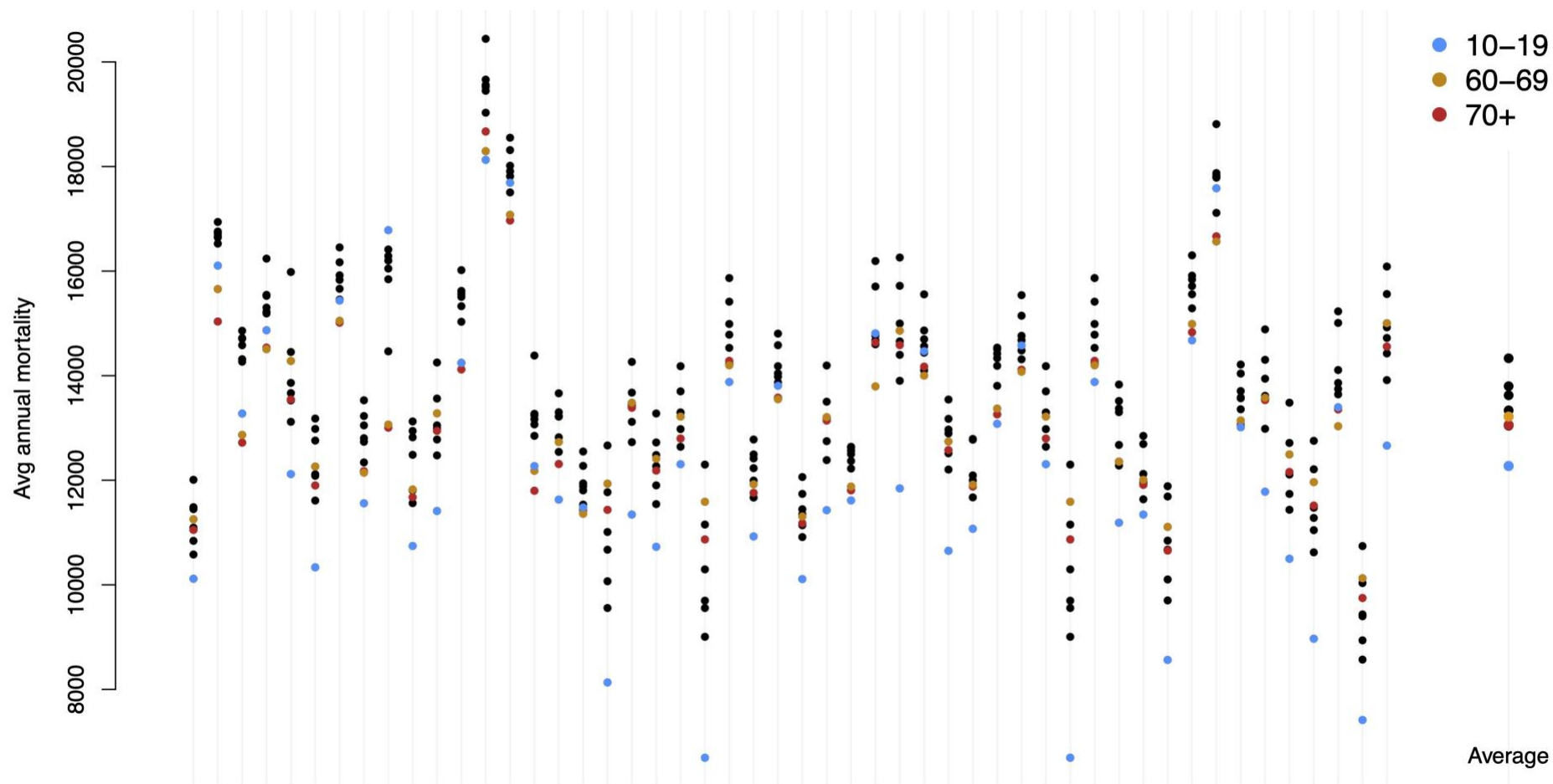


Figure S13. Average annual mortality under single-age prioritization for each age group across 50 model parameterizations. The 50 columns for each vaccine supply show the average annual mortality estimated for prioritizing each age group within each of the parameterizations. These points serve as counterparts to Figure 2, separated for each parameterization rather than averaged across parameterizations. Key age groups (10-19, 60-69, and 70+) are highlighted in colors. Figure S14 shows the number of parameterizations for which each age group yields the lowest mortality under a single-age prioritization strategy.

Figure S13 cont.

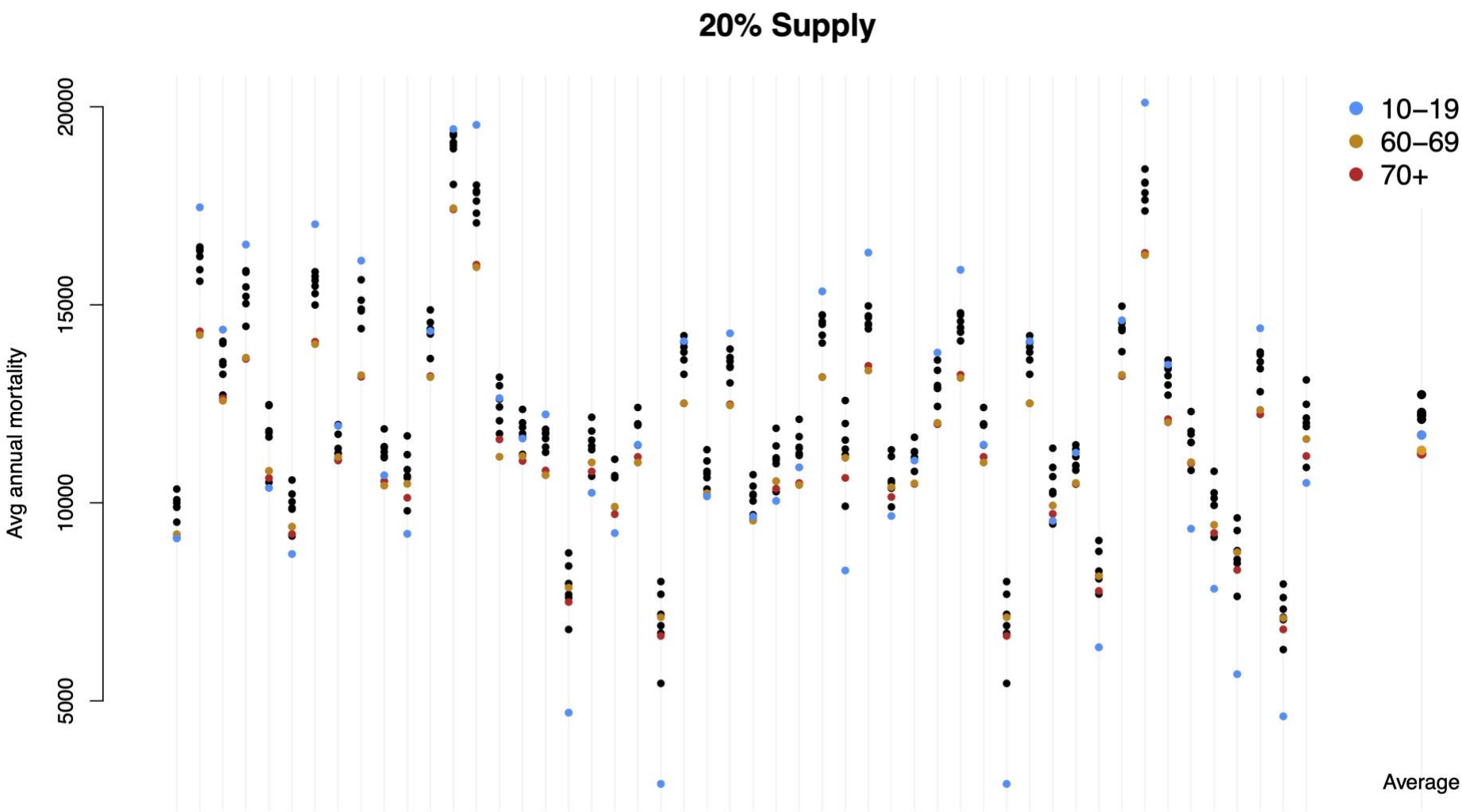


Figure S13 cont.

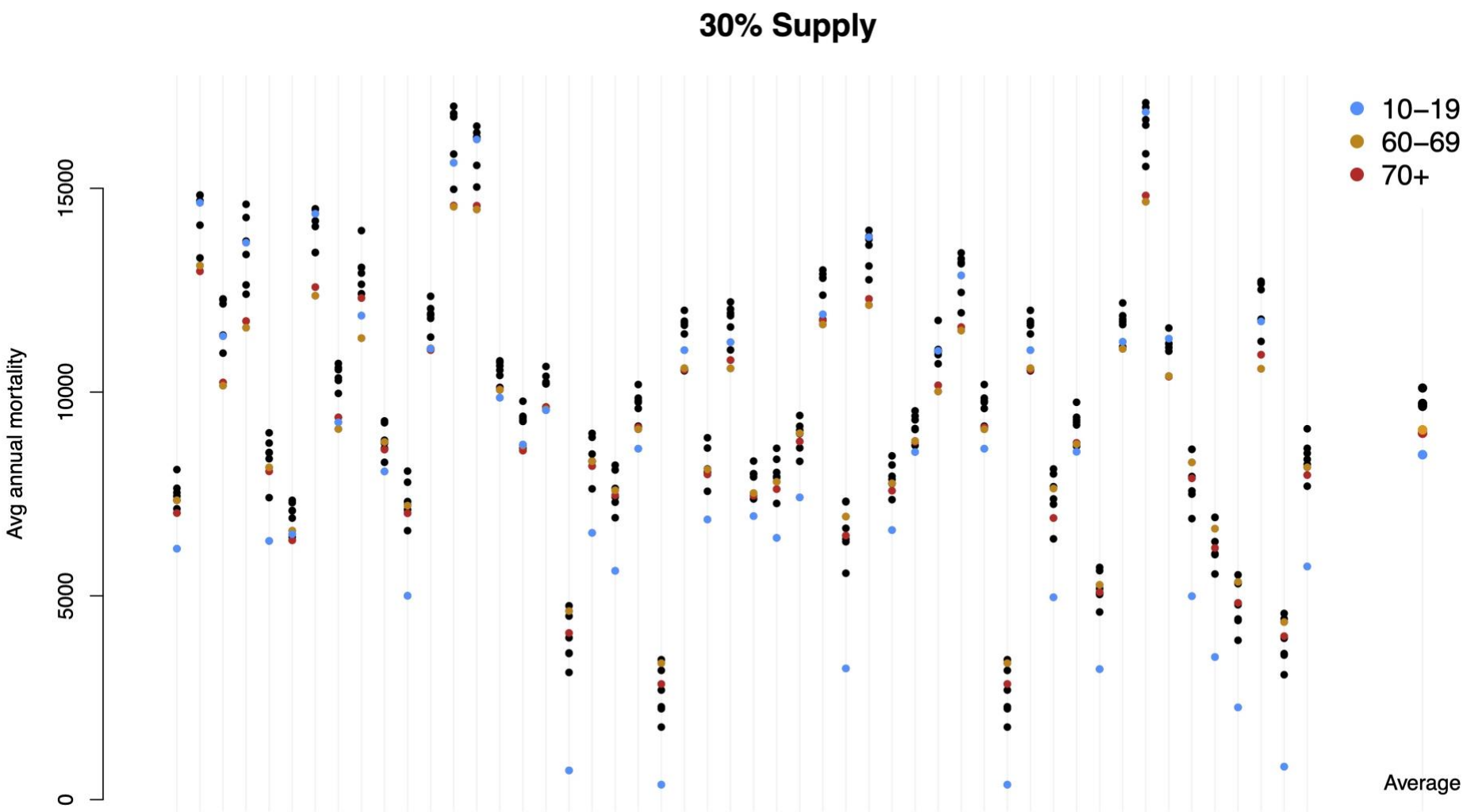


Figure S13 cont.

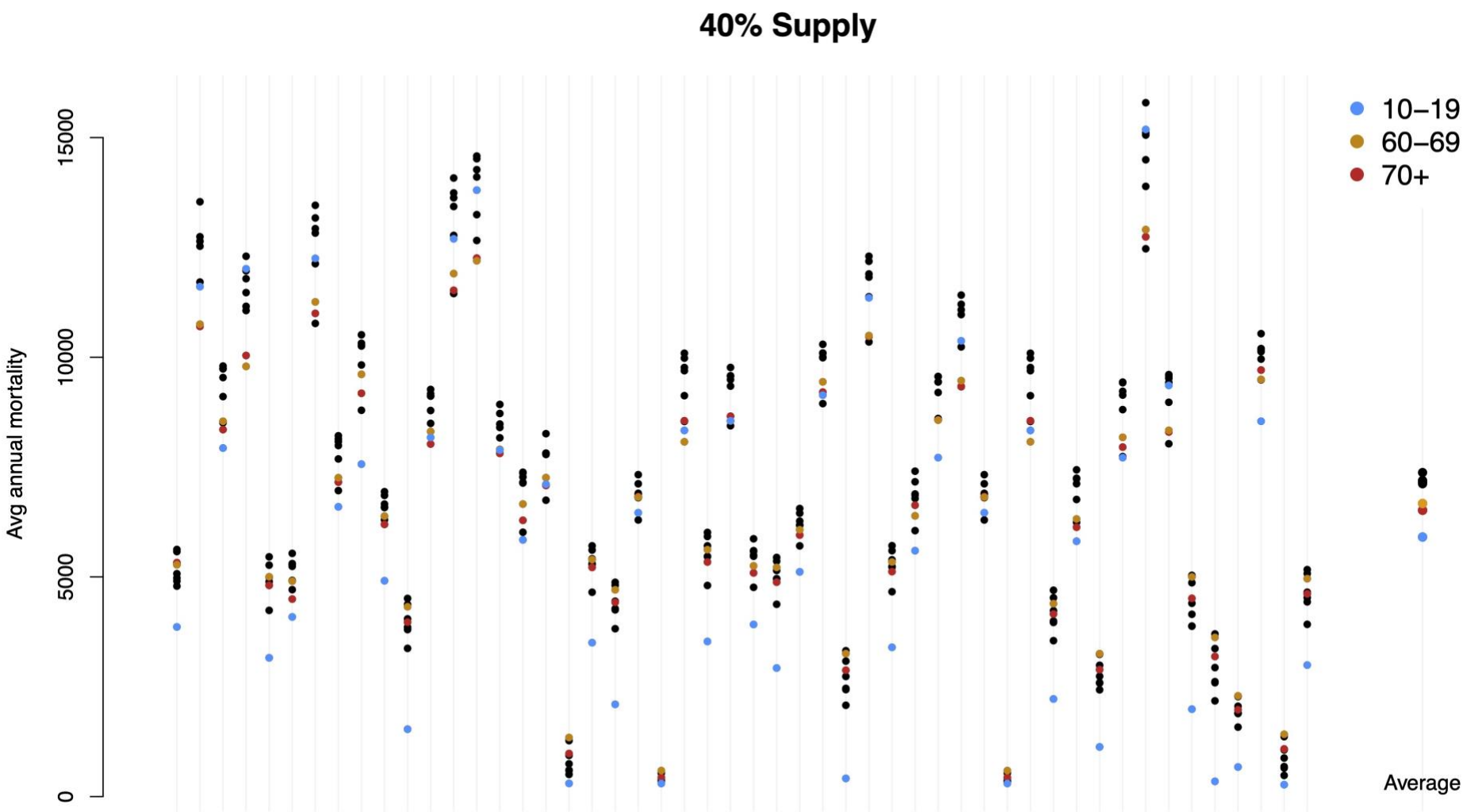


Figure S13 cont.

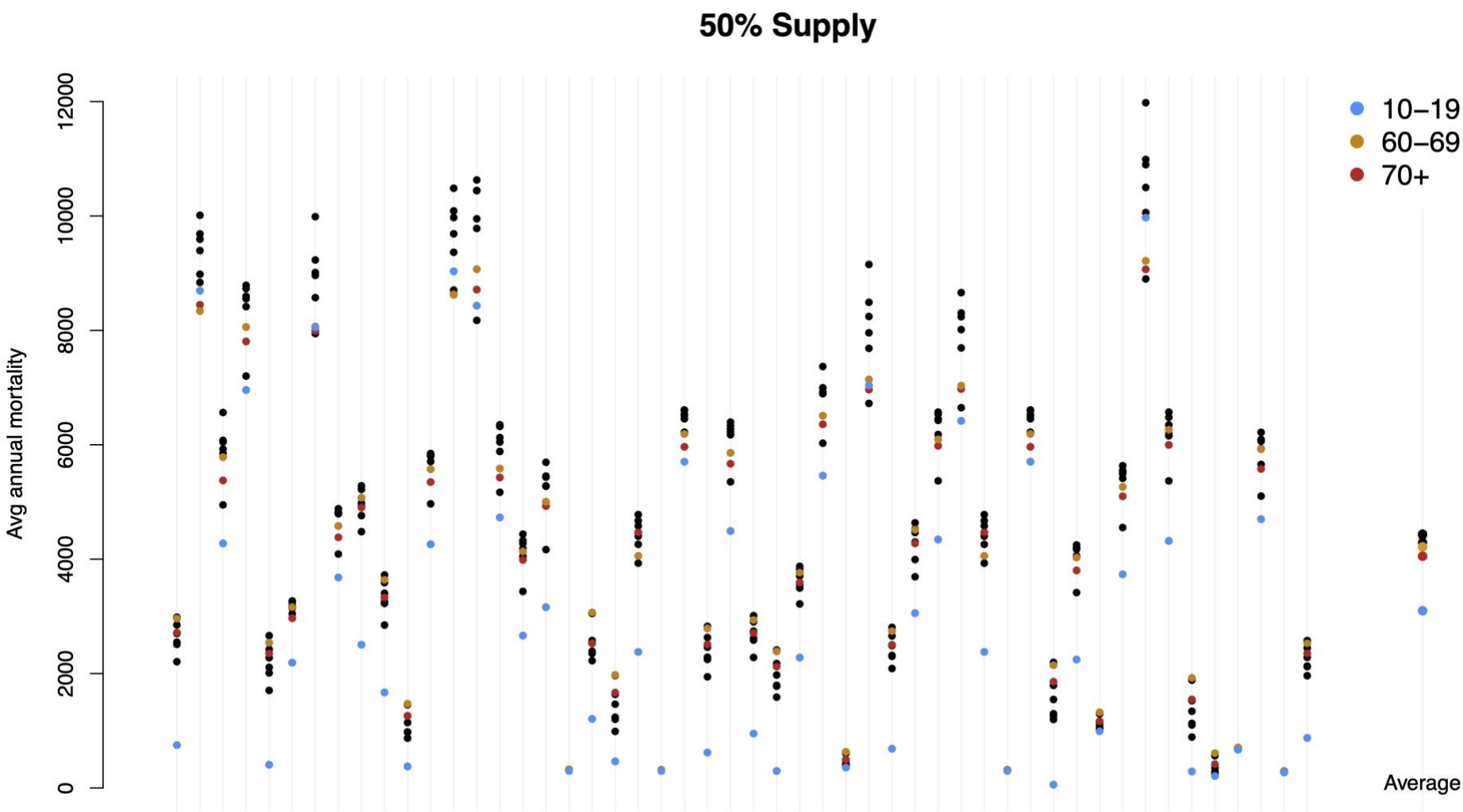


Figure S13 cont.

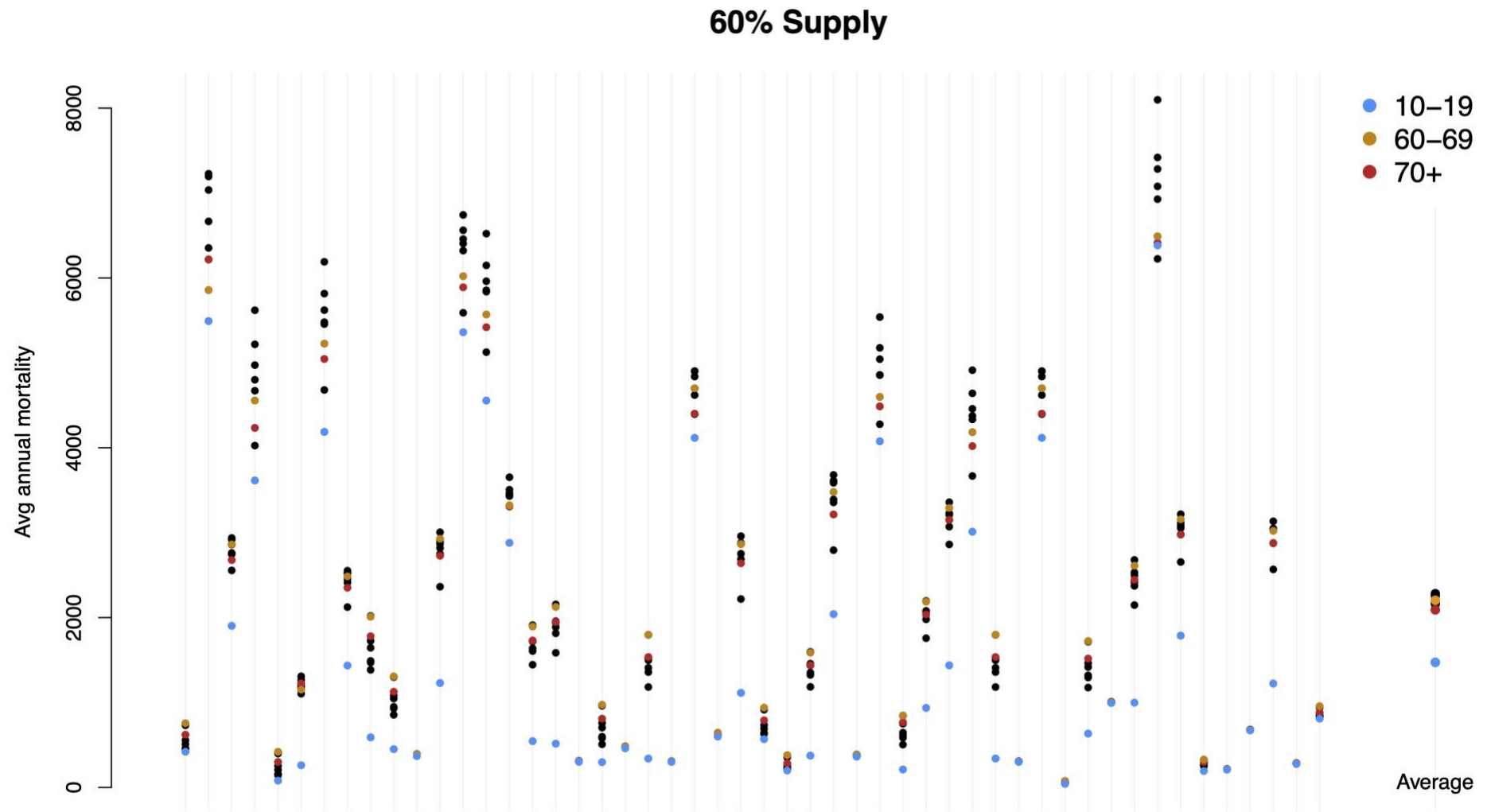


Figure S13 cont.

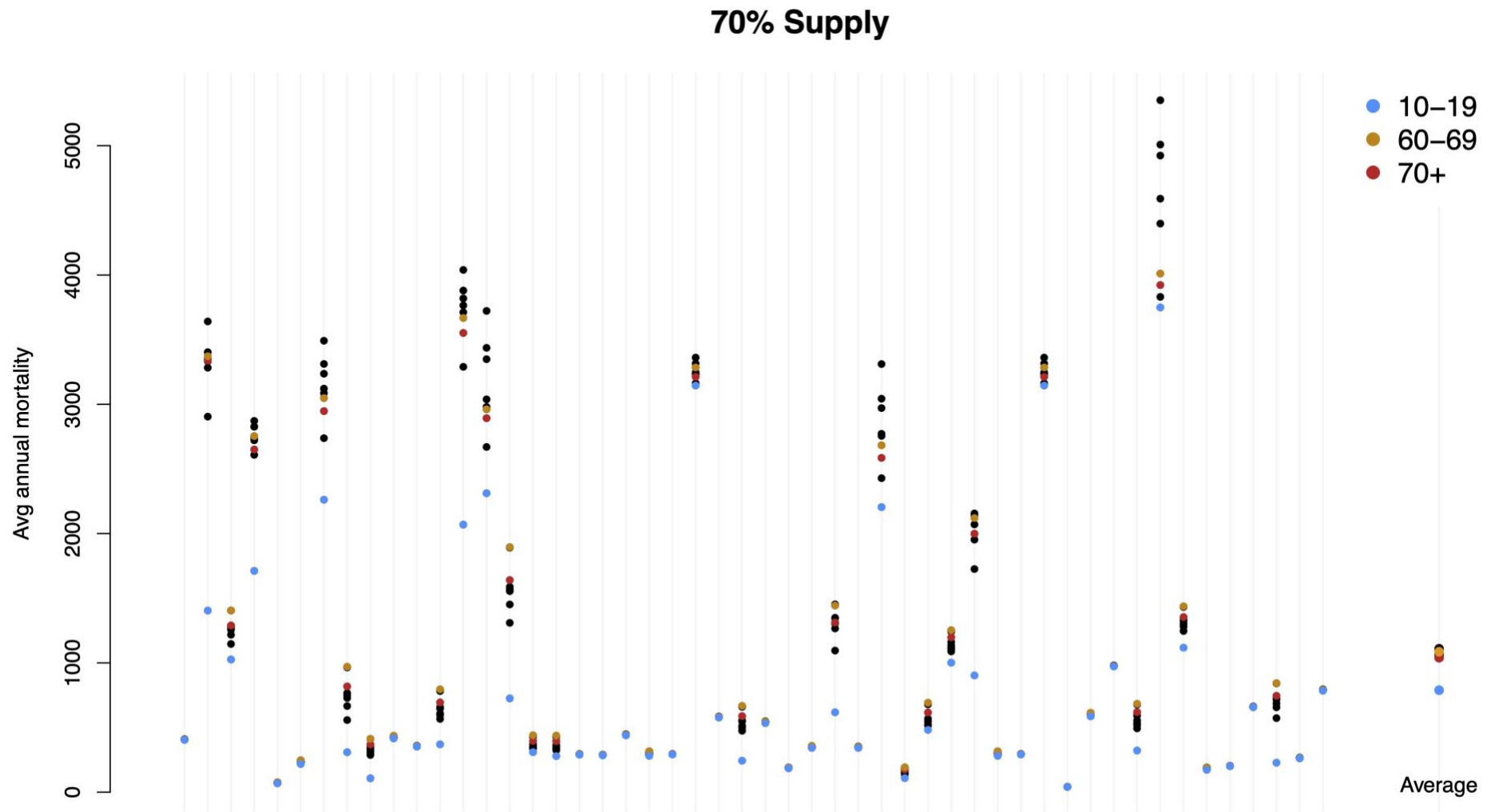


Figure S13 cont.

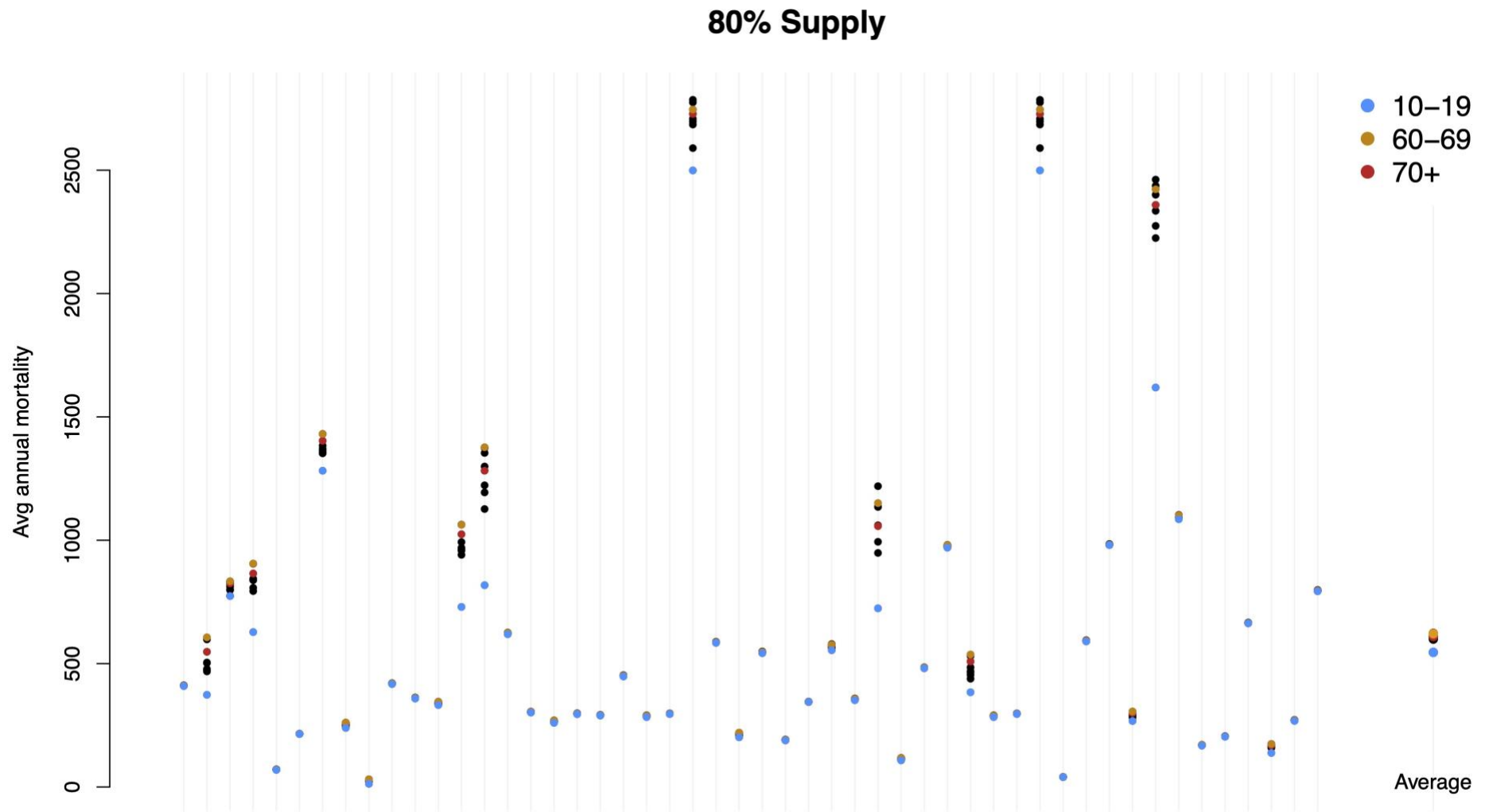
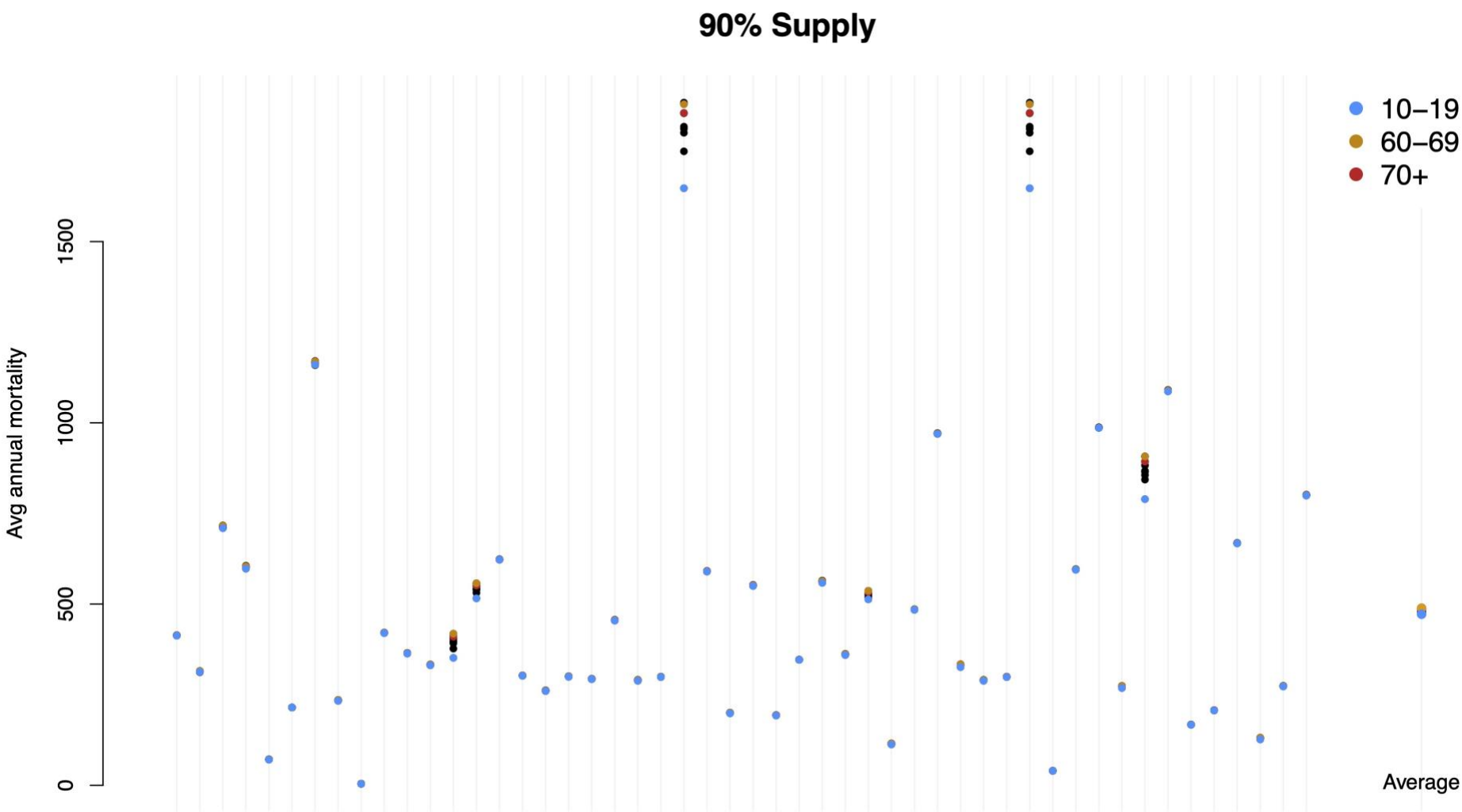


Figure S13 cont.



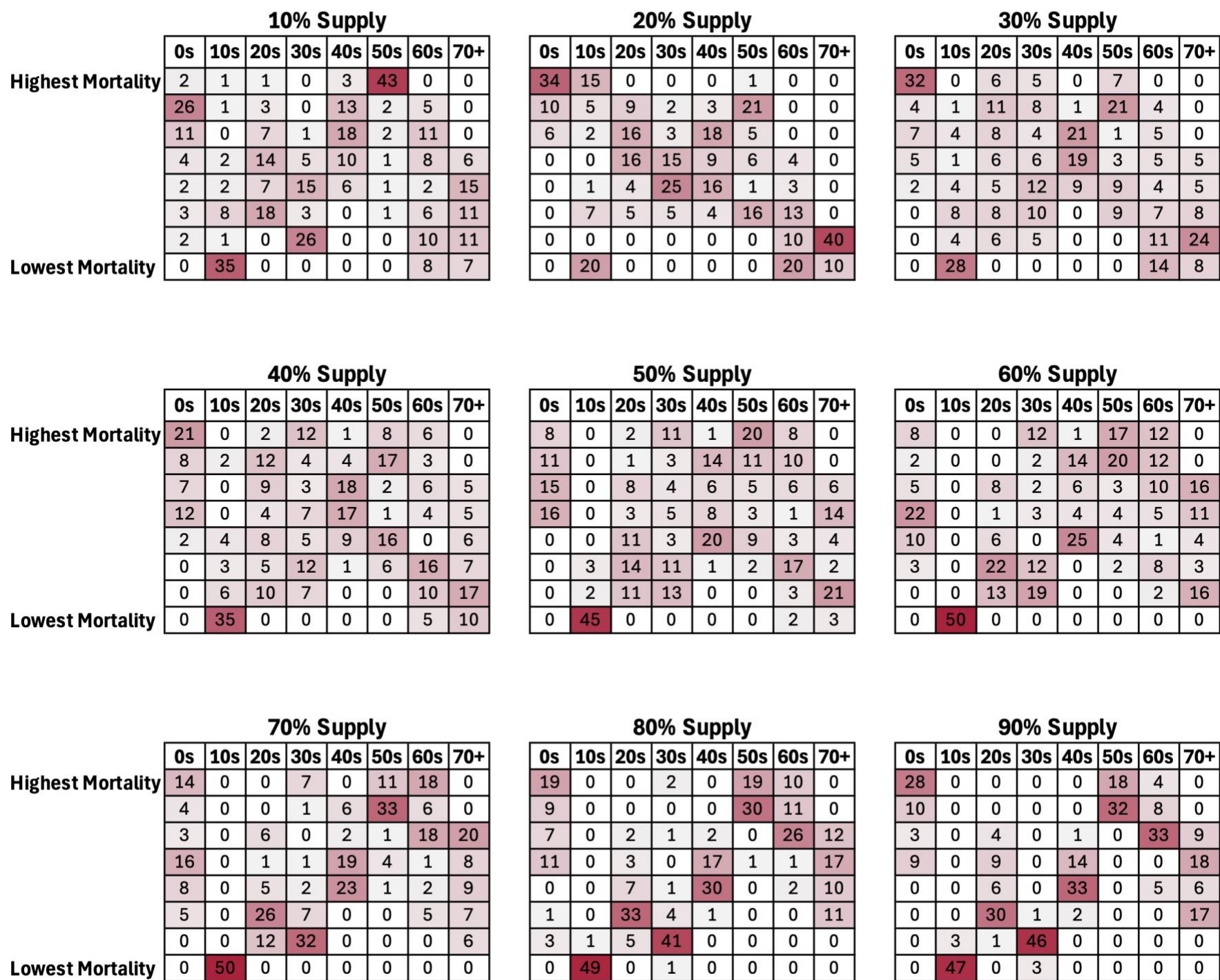


Figure S14. Frequency of ranks of each age group when prioritized singly for vaccination among 50 model parameterizations. Within each panel for a single vaccine supply, the frequency of parameterizations where each age group, when prioritized singly for vaccination, leads to each ranked position for annual mortality. Colors are indicated by the number of parameterizations where each age group lead to each ranking, where higher values indicate greater consistency across the parameterizations.

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