

Supplementary Material: High dose inactivated influenza vaccine inconsistently improves heterologous antibody responses in an elderly human cohort

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Reproducibility instructions

In order to reproduce our results, you should first download the archived repo from Zenodo (here: <https://doi.org/10.5281/zenodo.12666976>) or clone the Git repository (hosted on GitHub here: <https://github.com/ahgroup/Billings-2024-HD-Heterologous>). (You can also download the repository as a zipped folder from the GitHub page). If you use different software or package versions than what we used, or run the results in a different order, you may get errors or inconsistent results.

We ran the analysis on a Windows 10 Enterprise 64-bit (build 19045) machine with 64 GB RAM and a 36-core processor. Any statements we make about the execution time of code will vary across machines, especially if the hardware is different from these specs.

Before you can reproduce our results you will need to install the following software requirements.

- R version 4.4.1, available from <https://cran.r-project.org/>.
- RTools 4.4, also available from CRAN.
- The RStudio IDE, available from <https://posit.co/download/rstudio-desktop/>. We used version 2023.12.1+402 Ocean Storm (desktop).
- Quarto version 1.5.24, available from <https://quarto.org/>.
- Version 1.0.7 of the `renv` package for R, available from <https://cran.r-project.org/web/packages/renv/index.html>.

With the software installed, follow these instructions to reproduce our results.

1. Open the `SD-HD-flu-vaccine.Rproj` file in RStudio.
2. Once `renv` initializes, run the command `renv::restore()` in the Console in order to begin installing the required packages. If you have issues at this stage, you can also run `renv::deactivate()` and install the packages manually. However, if you do not use `renv` or use different package versions than we did, the following instructions might not work for you.
3. (This step is optional. If you do not want to re-run the Bayesian models, you can ignore this step.) If you want to re-run the Bayesian models, you need to install `cmdstan` at this step. You should have the `cmdstanr` package installed if you successfully followed the `renv` instructions, and you can follow the `cmdstanr` quick start guide at <https://mc-stan.org/cmdstanr/articles/cmdstanr.html> to install `cmdstan`. Start at the section titled “Installing CmdStan”. Installing `cmdstan` can be difficult, so make sure to carefully read the instructions. If you have issues with the `cmdstan` path or installation, you may need to open a new R GUI or RStudio window as an administrator (on Windows), install version v1.0.8 of `cmdstanr` manually, and re-run the installation and path setting steps. If you still have issues, the Stan discourse forum (<https://discourse.mc-stan.org/>) is often an excellent place to ask for help.

4. Now you should be able to run our code files. All of the code files are located in the `code` directory. The code files are designed to run in the following order, although multiple steps can potentially be skipped since we provide our results along with the code.
 - `02-Data-Summary.R`: the input files for this code are provided and it does not take a long time to run. This file recreates many of our summary tables.
 - `03-Model-Fitting.R`: this code specifies the `brms` models, and runs the HMC sampling scheme for our bayesian regression models. **This code takes a very long time to execute.** You do not need to run this code to reproduce our model results, as we have provided the model fit files along with the code.
 - `04-Posterior-Summaries.R`: this code computes the (c)ACE estimates from the fitted models. You should be able to run this code without running script 03. **Running this code took about an hour for us**, but will provide time estimates after the first set of cACEs is calculated. Running this code will reconstruct the model fit files.
 - `05-Model-Results.R`: processes the (c)ACE estimates into figures for the manuscript. The `all-cates-combined.Rds` input file is produced by script 04 and is provided with our code.. You can produce all of our figures with the cleaned data and this file of estimates.
 - `06-Supplementary-Analyses.R`: contains additional calculations for the Supplementary Material. You can run the first part of the script, including the DAG and tables, with only the cleaned data, which is provided. You should (at minimum) run script 04 before this code to ensure the model fit files are reconstructed.
 - The `common-functions` directory contains various helper functions and declarations and running the code on its own is not very interesting, although it is possible as long as all of the packages are installed correctly.
5. If you have run all of the code files, you can reproduce an unformatted version of the manuscript and supplement by rendering the files `products/manuscript/manuscript.qmd` and `products/manuscript/supplement.qmd`. When you open these files in RStudio with Quarto installed, you will see a “Render” button in the GUI that will execute the appropriate Quarto commands for you.

Note that the script `01-Data-Processing.R` contains our code for obtaining the finalized data set released in the Supplement: you will not be able to run this file. We do not provide the input file, `clean-data.Rds` due to data sensitivity concerns. Instead we have provided the output files in the `data/processed` folder along with the code.

Expanded Methods

Causal model for confounding

Since we used observational data rather than clinical trial data to estimate the effect of vaccine dose on immunological responses, we needed to adopt a causal model to control for confounding. A confounder is any other factor which can affect both the treatment an individual receives (i.e., which dose they got) and the outcome. We represented our causal assumptions using a directed acyclic graph (DAG), shown in Figure 1.

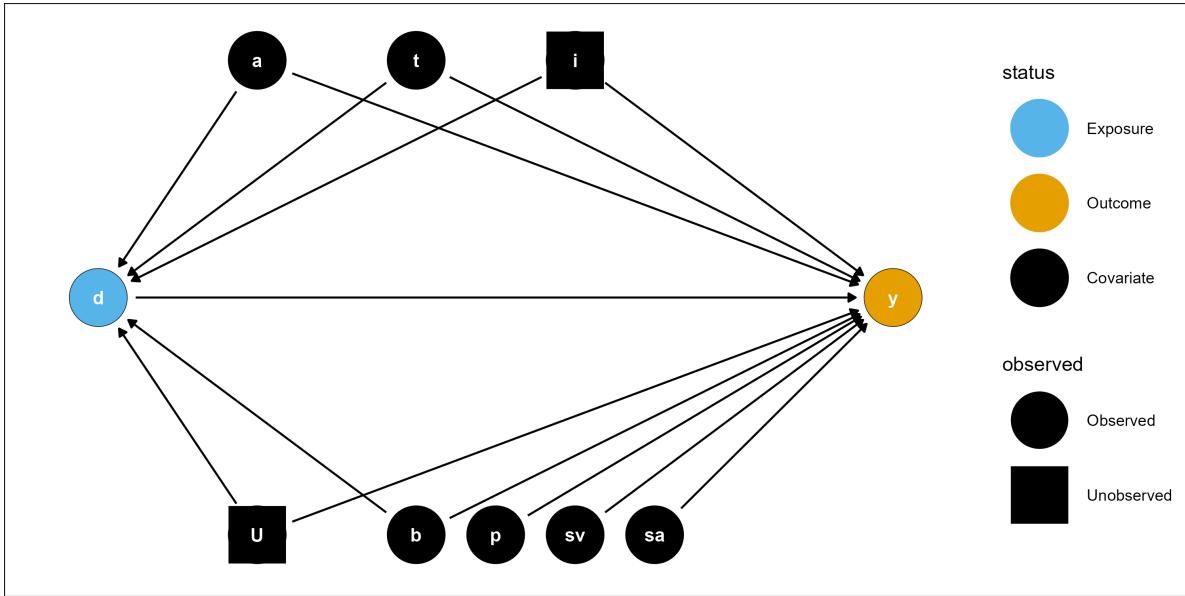


Figure 1: The DAG we adopted as our causal model. Nodes indicated variables and arrows follow the direction of causality, i.e., an arrow from X to Y indicates that X is a cause of Y .

In order to show the DAG nicely, the variable names are abbreviated by single letters. The letters in Figure 1 correspond to the following variables in our data (Table 1).

Table 1: Variable abbreviations used in the DAG.

Abbreviation	Variable
d	Vaccine dose
y	Immunological outcome
a	Age
t	Calendar time
i	Other individual effects

Abbreviation	Variable
U	Other unobserved confounders
b	Birth year
p	Pre-vaccination titer
sv	Strain included in vaccine
sa	Strain used for assay

We represent unobserved confounding in our DAG as the variable U . There are likely many confounders, like individual variables driving vaccine choice, which we cannot account for because they were not collected as part of the study we used. We attempted to control for unobserved confounding as best as possible by using a random effects model structure which can absorb part of the effect of unobserved confounders by modeling between-individual variability (which we represent as i in the DAG). Not all unobserved confounding effects can be absorbed by individual random effects, but some, such as for demographic characteristics like sex and race, potentially can be.

Even though not all of the variables shown are confounders (p , sv , and sa are only causes of the outcome in our DAG), we include sv and sa so we can obtain stratum-specific effects for those variables. Controlling for p does not open any backdoor paths (under our assumed causal model), so since p is a cause of the outcome we can include p in the model to potentially improve the efficiency of our estimates.

Model formula

The model formula for our hierarchical models was chosen based on *a priori* covariate information from our causal model, along with constraints induced by the estimability of random effects. We elected not to include interaction terms or any other nuisance covariates due to the complexity of the model. Notably, our model is unlikely to converge under frequentist maximum likelihood estimation, such as by the `nlme` R package, or other similar methods. The random effects in the model are overdetermined, which leads to near-zero (boundary) estimates of random effect covariance terms, which prevents the maximum likelihood model from reaching convergence. However, having random effects which are all similar does not prevent the NUTS algorithm implemented by Stan/`brms` from exploring the implied posterior distribution.

We specified our models in `brms` using the following model formula:

```
outcome ~ dose +
  s(birth_year_c, k = 5) + s(age_c, k = 5) +
  s(log_pretiter, k = 5) + s(year_c, k = 5, by = study) +
  (1 | id) + (1 | study) +
```

```
(1 + dose | strain_type) + (1 + dose | strain_type:strain_name) +
(1 + dose | vaccine_name) + (1 + dose | vaccine_name:strain_type).
```

The `brms` model syntax is explained more fully in the `brms` documentation, but we will briefly explain the model formula. The `outcome ~` specification declares that `outcome` is the outcome variable in the model, and everything after the `~` will be an independent variable. The term `dose` specifies a fixed effect of the variable `dose`, which by default will use indicator encoding (as will all qualitative variables). The model also includes a global intercept term by default.

All of the terms which look like `s(variable_name, k = 5)` specify smoothing splines. The smoothing spline basis matrix is constructed by the `mgcv` package (CITE) before being passed to the Stan code generated by `brms`, and so the smoothing splines are parametrized in the same way as for frequentist models. We used penalized thin-plate bases with $k = 5$ basis functions – since some of our predictor variables are integer-valued, choosing a low value of k provides reasonable flexibility for modeling nonlinear relationships while preventing the spline from being overdetermined. Finally, the specification `by = study` in the smoothing term for the variable `year_c` fits separate smoothing splines over the variable `year_c` for each stratum defined by the `study` variable. Since the three different studies did not all align temporally, we allowed the effect to be

Finally, all the terms in parenthesis with vertical bars (`|`) indicate random or varying effect terms. A `(1 | g)` term indicates a varying intercept for each unique level of the variable `g`, while a `(1 + v | g)` indicates a random effect of the variable `v`, which is allowed to differ for each unique level of the group variable `g`. Our model includes random intercepts for individuals (`id`) and the three different studies represented in our data (`study`), which allows all individuals and each of the studies to have different baseline effects on the model outcome. When the varying intercept and slope are specified together, they are assumed to be correlated, and the covariance matrix for the random effects is estimated.

We also include random intercepts for each `strain_type`, which refers to the influenza strain used to conduct an HAI assay: for our model, this is either H1N1 or H3N2. Furthermore, the specification `(1 + dose | strain_type) + (1 + dose | strain_type:strain_name)` adds random effects (on both the baseline and the effect of dose) for `strain_type`, and for `strain_name` nested within the `strain_type`. In our dataset, `strain_name` refers to the specific strain that was used to conduct an HAI assay. In other words, the random effects for all H1N1 strains are allowed to share information, and the random effects for all H3N2 strains are allowed to share information, but information cannot be borrowed across the strain types. The similar terms for `vaccine_name` and `strain_type` imply the same effects, but varying by the strain that was used in the vaccine formulation an individual received, rather than the strain used for the HAI assay.

The model is complicated, and not all combinations of random effects are observed in our data (in fact, they cannot be due to the update schedule of the influenza vaccine). That means

our random effects are neither completely nested nor completely crossed, but we allow random effects to be correlated with each other where appropriate.

Finally, the variable names specified with `_c` as a suffix have been centered to improve numerical estimation of the model. We performed all data transformation steps like log transformations and centering prior to passing any data to `brms` or Stan.

Model likelihood and priors

For the post-vaccination titer and titer increase outcomes, we used a Gaussian (Normal distribution) likelihood function for the model. Letting the outcome be y , we assumed that

$$y_i \sim \text{Normal}(\mu_i, \sigma),$$

where σ is the residual variance, and μ_i is described by the `brms` equation above, which builds a model for the conditional mean of `y_i` given the predictor data.

For the linear models, we used the following priors:

$$\begin{aligned}\alpha_{(.)} &\sim \text{Normal}(0, 5) \\ \beta_{(.)} &\sim \text{Normal}(0, 5) \\ \sigma &\sim t^+(\nu = 3, 0, 1) \\ L_{(.)} &\sim \text{LKJ}(1)\end{aligned}$$

Here, $\alpha_{(.)}$ are the global intercept and all of the random intercept parameters, which `brms` calls parameters of class “Intercept”. The $\beta_{(.)}$ are the regression parameters, which `brms` calls parameters of class “b”. The parameter σ is the residual variance, which has a Half- t (the generalized location-scale Student’s t distribution) distribution because it can only be positive, and to allow for the possibility of a large unexplained variance. Finally, the $L_{(.)}$ parameters are cholesky factors of the random effects correlation matrixes, which `brms` calls parameters of class “cor”. We specify priors on the Cholesky factors of the correlation matrices rather than the correlation matrices themselves to improve numerical performance of the model and ensure our priors do not generate correlation matrices which are not positive semi-definite.

For the seroconversion and seroprotection outcomes, we used a Bernoulli likelihood with a logit link function. That is, we assumed that

$$\begin{aligned}y_i &\sim \text{Bernoulli}(p_i), \\ p_i &= \text{logit}^{-1}(\mu_i),\end{aligned}$$

where μ_i is again described by the right-hand side of the `brms` formula. For these models, we used similar priors as follows.

$$\begin{aligned}\alpha_{(.)} &\sim \text{Normal}(0, 1) \\ \beta_{(.)} &\sim \text{Normal}(0, 1) \\ L_{(.)} &\sim \text{LKJ}(1)\end{aligned}$$

Because our outcome is fitted on the logit scale for the binary outcomes, we have to reduce the width of the priors. Using these relatively narrow priors actually gives a more uniform prior distribution of effects, because of the nonlinear transformation of the linear predictor, which severely deflates low values and severely inflates high values. There is no residual variance to estimate in the binary outcome models.

Model fitting

We implemented our models in `brms` [1,2], an R package which interfaces with the `cmdstanr` R package [3] and the `cmdstan` interface to the Stan probabilistic programming language [4]. Stan is a programming language designed to efficiently implement Hamiltonian Monte Carlo (HMC) for sampling from the posterior distribution of a Bayesian model [5]. HMC is a modern method which improves upon several limitations of other MCMC methods (such as random walk Metropolis-Hastings or Gibbs sampling) for models with continuous parameters.

We sampled all of our models across 16 chains (in parallel), with 500 warmup iterations and 1250 sampling iterations per chain, for a total of 20000 post-warmup samples per model. We increased the adaptive delta to 0.99 (which controls the ratio of accepted Metropolis proposals; increasing this parameter helps to prevent divergent transitions). We also seed the seed for each HMC run, but otherwise we used the default `cmdstan` control parameters.

cACE calculation

Our primary measure of effect size after fitting the model was the (C)ACE, or (Conditional) Average Causal Effect. The cACE represents the difference in model predictions for the two counterfactual potential outcomes. Let y_i be the observed outcome for individual i , and let t_i be the treatment for individual i (where $t_i \in \{\text{SD}, \text{HD}\}$). Using our fitted model, we can predict two counterfactual potential outcomes for individual i , which we call $\hat{y}_i(\text{HD})$, the predicted outcome if an individual had received the HD vaccine, and $\hat{y}_i(\text{SD})$, the predicted outcome if an individual had received the SD vaccine. Even though only one of these potential outcomes corresponds to the actual observed data, we can make predictions for both using the model. The individual causal effect (ICE) for individual i is defined as

$$\tau_i = \hat{y}_i(\text{HD}) - \hat{y}_i(\text{SD}).$$

We can then summarize the posterior distribution of τ_i measurements to estimate the average causal effect (ACE). If the ACE is positive, then our model predicts that the HD vaccine elicits a stronger immune response on average in our study sample.

While the most common way to calculate the ACE is by taking the sample mean and associated 95% confidence interval over all of the calculated ICEs, in a Bayesian framework, we have k samples (in our specific case, 20000) from the posterior distribution of the ICE for each individual. We can pool these samples either all together to obtain the posterior distribution of the overall ACE for our sample, or we can pool samples together within strata to obtain estimates for various cACEs, where “conditional” refers to an observation being in a specific stratum (for example, all assays conducted on samples given by donors who had received a vaccine containing CA/09-like virus particles).

Specifically, we summarized all (c)ACEs in our study using the mean point estimate from the relevant posterior samples, along with the 95% highest density continuous interval (HDCI). We estimated the mean and HDCI using the `ggdist` R package [6,7], which (at the time of writing) calculates the HDCI using a CDF-bounded density estimator with a Gaussian kernel using the reflection method [8,9]. The density estimate is trimmed to the bounds of the data, the bandwidth is estimated using the Sheather-Jones Direct Plug-In method [10], and we evaluated the density estimator at 4096 grid points.

Effect size transformation from cACE calculation

The cACE (as described in a previous section) is calculated by taking a difference of predicted model outcomes. Since the model predictions are in units of log titer measurements (regardless of whether the outcome is post-vaccination titer or titer increase), the cACE is expressed in log titer units. In order to better communicate the effect size, we transformed the cACE. As before, let $\hat{y}_i(\text{SD})$ be the predicted treatment effect for individual i if that individual had received an SD vaccine, and let $\hat{y}_i(\text{HD})$ be the predicted treatment effect for individual i if that individual had received an HD vaccine. The estimated ICE is

$$\hat{\tau}_i = \hat{y}_i(\text{HD}) - \hat{y}_i(\text{SD}),$$

which represents the estimated benefit that individual i would receive from the HD vaccine. Our model generates a posterior distribution of the estimated ICE for each individual

The (c)ACE over the study sample is estimated as

$$\widehat{\text{ACE}}_i = E(\hat{\tau}_i) = E(\hat{y}_i(\text{HD}) - \hat{y}_i(\text{SD})),$$

and we compute this by pooling together the posterior distributions of the ICEs and summarizing them. However, each ICE is in log2-titer units, and so the ACE is also in log2-titer units. To facilitate interpretation, we can exponentiate (a monotone strictly increasing transformation) the estimated ACE to obtain an estimate in more interpretable titer units.

The transformed ACE, which we (arbitrarily) denote as $\widehat{\varphi}_i$ is then

$$\widehat{\varphi}_i = 2^{\tau_i} = 2^{E(\widehat{y}_i(\text{HD}) - \widehat{y}_i(\text{SD}))},$$

and is in HAI titer units. This number represents the average treatment effect as a ratio of fold changes, for the results presented in the main text. It can be interpreted analogously for the other three outcomes we used as sensitivity analyses in a later section of this Supplement.

Supplementary results

Descriptive analysis

First, we conducted a descriptive analysis of the outcomes, stratified by vaccine dose. In order to determine how different the effect of dose was across the different vaccines and assay strains, we further conducted stratified analyses.

Birth year and age summary statistics

Table Table 2 shows the number of unique individuals who were recruited at each study site, along with summaries of their age at first enrollment in the study and birth year. The ages at enrollment and birth years were very similar across the three study sites.

Table 2: Number of unique individuals who were recruited at each study site, along with summaries of the age at first enrollment and birth year of participants at each study site and overall.

Characteristic	FL, N = 52	PA, N = 83	UGA, N = 119	Overall, N = 254
Age at first enrollment, Median (Range)	68 (65 - 80)	68 (65 - 82)	68 (65 - 85)	68 (65 - 85)
Birth year, Median (Range)	1946 (1933 - 1951)	1945 (1932 - 1951)	1950 (1934 - 1956)	1948 (1932 - 1956)

Cohort demographics and assays by year

The study was collected at two different sites (PA and FL) from 2013/14 through 2016/17, but moved to the UGA site in January 2017. The demographic information stratified by study site is shown in Table 3. The FL study site gave fewer HD vaccinations, but there were no noticeable differences in the age or birth cohort of individuals from the three study sites.

Table 3: Demographics of the study sample stratified by the three study sites. The only season when all three study sites recruited individuals was 2016/17.

Characteristic	FL, N = 123	PA, N = 219	UGA, N = 326	Overall, N = 668
Season, n (%)				
2013 - 2014	20 (16)	36 (16)	0 (0)	56 (8)
2014 - 2015	35 (28)	57 (26)	0 (0)	92 (14)
2015 - 2016	35 (28)	63 (29)	0 (0)	98 (15)
2016 - 2017	33 (27)	63 (29)	15 (5)	111 (17)
2017 - 2018	0 (0)	0 (0)	38 (12)	38 (6)
2018 - 2019	0 (0)	0 (0)	19 (6)	19 (3)
2019 - 2020	0 (0)	0 (0)	90 (28)	90 (13)
2020 - 2021	0 (0)	0 (0)	83 (25)	83 (12)
2021 - 2022	0 (0)	0 (0)	81 (25)	81 (12)
Dose, n (%)				
SD	82 (67)	73 (33)	79 (24)	234 (35)
HD	41 (33)	146 (67)	247 (76)	434 (65)

The vaccine composition for each year is shown in Table 4.

Table 4: Composition of the Fluzone vaccine during each influenza season. The strains used were matched to ACIP/CDC recommendations, and were the same for both the SD and HD vaccine vormulations.

season	H1N1	H3N2
2013 - 2014	CA/09	TX/12
2014 - 2015	CA/09	TX/12
2015 - 2016	CA/09	Switz/13
2016 - 2017	CA/09	HK/14
2017 - 2018	MI/15	HK/14
2018 - 2019	MI/15	Sing/16

season	H1N1	H3N2
2019 - 2020	Bris/18	KS/17
2020 - 2021	GD/19	HK/19
2021 - 2022	Vic/19	Tas/20

The panel of historical assays used in each year is shown in Table 5.

Table 5: Number of assays performed using each component of the historical panel for a given season. Over the different seasons, strains were added and removed from the historical panel, indicated by the zeros in the table.

Subtype	Strain	13/14	14/15	15/16	16/17	17/18	18/19	19/20	20/21	21/22	Total
H1N1	SC/18	42	92	98	111	38	0	0	0	0	381
H1N1	PR/34	42	0	0	0	0	0	0	0	0	42
H1N1	Wei/43	42	92	98	111	38	0	0	0	0	381
H1N1	FM/47	42	92	98	111	38	0	0	0	0	381
H1N1	Den/57	42	92	98	111	38	0	0	0	0	381
H1N1	NJ/76	42	92	98	111	38	0	0	0	0	381
H1N1	USSR/77	42	92	98	111	38	0	0	0	0	381
H1N1	Bra/78	42	0	0	111	38	0	0	0	0	191
H1N1	Chi/83	42	92	98	111	38	19	90	0	0	490
H1N1	Sing/86	56	92	98	111	38	19	0	0	0	414
H1N1	TX/91	56	92	98	111	38	19	0	0	0	414
H1N1	Bei/95	56	92	98	111	38	19	0	0	0	414
H1N1	NC/99	55	92	98	111	38	19	0	0	0	413
H1N1	SI/06	56	92	98	111	38	19	0	0	0	414
H1N1	Bris/07	56	92	98	111	38	19	90	0	0	504
H1N1	CA/09	56	92	98	111	38	19	90	83	81	668
H1N1	CA/78	0	92	98	0	0	0	0	0	0	190
H1N1	MI/15	0	0	0	111	38	19	90	83	0	341

Subtype	Strain	13/14	14/15	15/16	16/17	17/18	18/19	19/20	20/21	21/22	Total
H1N1	Bris/18	0	0	0	0	0	0	90	83	81	254
H1N1	GD/19	0	0	0	0	0	0	90	83	81	254
H1N1	Vic/19	0	0	0	0	0	0	0	0	81	81
H3N2	HK/68	56	92	98	111	38	0	0	0	0	395
H3N2	PC/73	56	92	98	111	38	0	0	0	0	395
H3N2	TX/77	56	92	98	111	38	0	0	0	0	395
H3N2	MI/85	56	92	97	111	38	0	0	0	0	394
H3N2	Sich/87	42	92	97	111	38	0	0	0	0	380
H3N2	Shan/93	42	92	98	111	38	0	0	0	0	381
H3N2	Nan/95	42	92	98	111	38	0	0	0	0	381
H3N2	Syd/97	56	92	98	111	38	0	0	0	0	395
H3N2	Pan/99	56	92	98	111	38	19	90	0	0	504
H3N2	Fuj/02	42	92	98	0	0	0	0	0	0	232
H3N2	NY/04	56	92	98	111	38	19	0	0	0	414
H3N2	Br/07	42	0	0	0	0	0	0	0	0	42
H3N2	WI/05	56	92	98	111	38	19	0	0	0	414
H3N2	Per/09	56	92	98	111	38	19	0	0	0	414
H3N2	Vic/11	56	92	98	111	38	19	0	0	0	414
H3N2	TX/12	56	92	98	111	38	19	90	0	0	504
H3N2	Switz/13	36	91	98	111	38	19	90	0	0	483
H3N2	Uru/07	0	92	98	111	38	19	0	0	0	358
H3N2	HK/14	0	91	98	111	38	19	90	83	81	611
H3N2	Sing/16	0	0	0	0	38	19	90	83	81	311
H3N2	KS/17	0	0	0	0	0	0	90	83	81	254
H3N2	HK/19	0	0	0	0	0	0	90	83	81	254
H3N2	SA/19	0	0	0	0	0	0	90	0	81	171
H3N2	Tas/20	0	0	0	0	0	0	0	0	81	81

Subtype	Strain	13/14	14/15	15/16	16/17	17/18	18/19	19/20	20/21	21/22	Total
H3N2	Dar/21	0	0	0	0	0	0	0	0	81	81

We used the abbreviated names of each strain throughout the paper in order to simplify tables and graphics. The complete strain names along with the abbreviated names are shown in Table 6.

Table 6: Abbreviated strain names used in figures and tables, along with complete strain names.

H1N1		H3N2	
Strain name	Short name	Strain name	Short name
A/H1N1/South Carolina/1/1918	SC/18	A/H3N2/Hong Kong/8/1968	HK/68
A/H1N1/Puerto Rico/8/1934	PR/34	A/H3N2/Port Chalmers/1/1973	PC/73
A/H1N1/Weiss/43	Wei/43	A/H3N2/Texas/1/1977	TX/77
A/H1N1/Fort Monmouth/1/1947	FM/47	A/H3N2/Mississippi/1/1985	MI/85
A/H1N1/Denver/1957	Den/57	A/H3N2/Sichuan/2/1987	Sich/87
A/H1N1/New Jersey/8/1976	NJ/76	A/H3N2/Shangdong/9/1993	Shan/93
A/H1N1/Ussr/90/1977	USSR/77	A/H3N2/Nanchang/933/1995	Nan/95
A/H1N1/Brazil/11/1978	Bra/78	A/H3N2/Sydney/5/1997	Syd/97
A/H1N1/California/10/1978	CA/78	A/H3N2/Panama/2007/1999	Pan/99
A/H1N1/Chile/1/1983	Chi/83	A/H3N2/Fujian/411/2002	Fuj/02
A/H1N1/Singapore/6/1986	Sing/86	A/H3N2/New York/55/2004	NY/04
A/H1N1/Texas/36/1991	TX/91	A/H3N2/Brisbane/10/2007	Br/07
A/H1N1/Beijing/262/1995	Bei/95	A/H3N2/Wisconsin/67/2005	WI/05
A/H1N1/New Caledonia/20/1999	NC/99	A/H3N2/Uruguay/716/2007	Uru/07
A/H1N1/Solomon Islands/3/2006	SI/06	A/H3N2/Perth/16/2009	Per/09
A/H1N1/Brisbane/59/2007	Bris/07	A/H3N2/Victoria/361/2011	Vic/11
A/H1N1/California/07/2009	CA/09	A/H3N2/Texas/50/2012	TX/12
A/H1N1/Michigan 45/2015	MI/15	A/H3N2/Switzerland/9715293/2013Switz/13	
A/H1N1/Brisbane/02/2018	Bris/18	A/H3N2/Hong Kong/4801/2014	HK/14

H1N1		H3N2	
Strain name	Short name	Strain name	Short name
A/H1N1/Guangdong-Maonan/SWL1536/201	GD/19	A/H3N2/Singapore/infimh-0019/2016	Sing/16
A/H1N1/Victoria/2570/2019	Vic/19	A/H3N2/Kansas/14/2017	KS/17
		A/H3N2/Hong Kong/2671/2019	HK/19
		A/H3N2/South Australia/34/2019	SA/19
		A/H3N2/Tasmania/503/2020	Tas/20
		A/H3N2/Darwin/9/2021	Dar/21

Outcome summaries

For each outcome (and additionally the pre-vaccination titer), we computed crude summary statistics for the SD and HD groups in order to obtain a measure of the crude effect size. For the pre-vaccination titer, post-vaccination titer, and fold change, we computed the geometric mean and geometric SD, while for the seroprotection and serconversion, we computed the number and percentage of individuals for which each event occurred. We also computed standardized mean differences (SMDs) to compare the groups using the method of Yang and Dalton [11] using the R package `smd` [12].

We did not further stratify by each assay strain during the crude analysis, because the low sample size and number of comparisons would greatly inflate the amount of noise in the analysis, and understanding the stratified results would be very difficult. Notably, SMDs can be roughly interpreted by the guidelines shown in Table 7, although these should not be strictly or decisively used to make decisions based on the qualitative guidelines alone [13,14].

Table 7: Suggested qualitative interpretations of the Cohen’s d effect sizes represented by our SMD calculations. Note that these are only rough guidelines.

Cohen’s d	Interpretation
0.01	Very small
0.20	Small
0.50	Medium
0.80	Large
1.20	Very large
2.0	Huge

Pre-vaccination titer

Table 8 shows the crude analysis of the pre-vaccination titer. In contrast to the results shown in the main paper, the overall effect and the effects for all combined H1N1 and H3N2 strains are both near zero. However, for some vaccine strains, the pre-vaccination titer was clearly higher for the HD group than the SD group, potentially due to the effect of receiving HD vaccines in multiple years. We used a flexible smoothing spline to control for the effect of pre-vaccination titer in our main model to reduce confounding by pre-vaccination titer in our main results.

Table 8: Crude analysis of the pre-vaccination titer, stratified by dose.

Subtype	Vaccine strain	n ¹		Pre-vaccination titer ²		
		SD	HD	SD	HD	SMD ³
Overall	Overall	6,668	9,360	16.27 (± 3.31)	16.29 (± 3.21)	0.00 (-0.03, 0.03)
H1N1	Overall	3,082	4,288	13.40 (± 3.04)	12.94 (± 2.78)	-0.03 (-0.08, 0.01)
	CA/09	2,453	2,942	14.53 (± 3.17)	13.96 (± 2.88)	-0.04 (-0.09, 0.02)
	MI/15	451	328	10.46 (± 2.43)	15.07 (± 2.84)	0.38 (0.23, 0.52)
	Bris/18	126	414	8.16 (± 2.14)	7.66 (± 2.06)	-0.08 (-0.28, 0.11)
	GD/19	28	304	9.28 (± 2.09)	12.03 (± 2.57)	0.31 (-0.08, 0.70)
	Vic/19	24	300	7.49 (± 1.71)	11.57 (± 2.34)	0.61 (0.20, 1.03)
H3N2	Overall	3,586	5,072	19.22 (± 3.46)	19.79 (± 3.46)	0.02 (-0.02, 0.07)
	TX/12	1,544	972	19.42 (± 3.43)	22.34 (± 3.56)	0.11 (0.03, 0.19)
	Switz/13	720	1,042	15.90 (± 3.11)	17.04 (± 3.22)	0.06 (-0.04, 0.15)
	HK/14	974	1,597	20.16 (± 3.62)	24.06 (± 3.66)	0.14 (0.06, 0.22)
	Sing/16	110	80	36.39 (± 4.62)	21.07 (± 3.93)	-0.38 (-0.67, -0.09)
	KS/17	168	552	19.92 (± 3.39)	14.80 (± 2.94)	-0.26 (-0.43, -0.09)
	HK/19	28	304	23.20 (± 2.54)	21.46 (± 3.34)	-0.07 (-0.46, 0.31)
	Tas/20	42	525	15.87 (± 2.88)	15.08 (± 3.27)	-0.05 (-0.36, 0.27)

¹Total number of HAI assays across all assay strains and seasons.

²Pre-vaccination HAI titer. Geometric mean (\pm geometric standard deviation).

³Standardized mean difference (HD - SD); SMD (95% CI).

Post-vaccination titer

Table 9 shows the crude dose-stratified analysis of the post-vaccination titer outcome. We saw an overall weakly positive effect of the HD vaccine, compared to the SD vaccine, which matched what we saw in our primary adjusted analysis of the fold change. Notably, some strains showed a noticeable negative effect of the HD vaccine, which tended to correspond with the strains where the HD group had higher pre-vaccination titers (Table 8) in the crude analysis.

Table 9: Crude analysis of the post-vaccination titer, stratified by dose.

Subtype	Vaccine strain	n ¹		Post-vaccination titer ²			SMD ³
		SD	HD	SD	HD	SMD ³	
Overall	Overall	6,668	9,360	24.68 (± 4.10)	28.99 (± 4.01)	0.12 (0.08, 0.15)	
H1N1	Overall	3,082	4,288	17.29 (± 3.35)	20.09 (± 3.24)	0.13 (0.08, 0.17)	
	CA/09	2,453	2,942	18.44 (± 3.40)	19.92 (± 3.22)	0.06 (0.01, 0.12)	
	MI/15	451	328	11.68 (± 2.74)	19.01 (± 3.19)	0.45 (0.30, 0.59)	
	Bris/18	126	414	16.86 (± 3.82)	14.07 (± 3.01)	-0.15 (-0.35, 0.05)	
	GD/19	28	304	21.02 (± 2.22)	26.29 (± 2.96)	0.24 (-0.15, 0.62)	
	Vic/19	24	300	33.64 (± 3.13)	28.95 (± 3.49)	-0.13 (-0.54, 0.29)	
H3N2	Overall	3,586	5,072	33.52 (± 4.47)	39.53 (± 4.39)	0.11 (0.07, 0.15)	
	TX/12	1,544	972	28.48 (± 3.96)	40.86 (± 4.00)	0.26 (0.18, 0.34)	
	Switz/13	720	1,042	39.09 (± 5.33)	45.21 (± 5.54)	0.09 (-0.01, 0.18)	
	HK/14	974	1,597	32.43 (± 4.55)	41.23 (± 4.41)	0.16 (0.08, 0.24)	
	Sing/16	110	80	52.78 (± 4.80)	31.93 (± 4.01)	-0.34 (-0.63, -0.05)	
	KS/17	168	552	60.43 (± 4.21)	40.81 (± 4.09)	-0.28 (-0.45, -0.10)	
	HK/19	28	304	44.16 (± 2.70)	35.37 (± 3.37)	-0.20 (-0.59, 0.19)	
	Tas/20	42	525	50.40 (± 3.82)	26.71 (± 3.61)	-0.49 (-0.80, -0.17)	

¹Total number of HAI assays across all assay strains and seasons.

²Post-vaccination HAI titer. Geometric mean (\pm geometric standard deviation).

³Standardized mean difference (HD - SD); SMD (95% CI).

Fold change

The crude analysis of the fold change (Table 10) was similar to our main adjusted analysis. The only qualitatively different result was the significant overall SMD, and the significant SMDs for all H1N1 and all H3N2 strains, indicating a small positive effect of the HD vaccine. These results are consistent with our main adjusted analysis.

Table 10: Crude analysis of the fold change, stratified by dose.

Subtype	Vaccine strain	n ¹		Fold change ²			SMD ³
		SD	HD	SD	HD		
Overall	Overall	6,668	9,360	1.52 (± 2.42)	1.78 (± 2.51)	0.18 (0.15, 0.21)	
H1N1	Overall	3,082	4,288	1.29 (± 2.19)	1.55 (± 2.24)	0.23 (0.19, 0.28)	
	CA/09	2,453	2,942	1.27 (± 2.19)	1.43 (± 2.15)	0.15 (0.10, 0.21)	
	MI/15	451	328	1.12 (± 1.68)	1.26 (± 1.83)	0.22 (0.07, 0.36)	
	Bris/18	126	414	2.07 (± 3.05)	1.84 (± 2.15)	-0.12 (-0.32, 0.08)	
	GD/19	28	304	2.26 (± 1.98)	2.19 (± 2.33)	-0.05 (-0.43, 0.34)	
	Vic/19	24	300	4.49 (± 2.48)	2.50 (± 2.84)	-0.60 (-1.02, -0.19)	
H3N2	Overall	3,586	5,072	1.74 (± 2.56)	2.00 (± 2.69)	0.14 (0.10, 0.18)	
	TX/12	1,544	972	1.47 (± 2.19)	1.83 (± 2.62)	0.25 (0.17, 0.33)	
	Switz/13	720	1,042	2.46 (± 3.12)	2.65 (± 3.44)	0.06 (-0.03, 0.16)	
	HK/14	974	1,597	1.61 (± 2.40)	1.71 (± 2.36)	0.07 (-0.01, 0.15)	
	Sing/16	110	80	1.45 (± 1.79)	1.52 (± 2.11)	0.07 (-0.22, 0.35)	
	KS/17	168	552	3.03 (± 3.19)	2.76 (± 2.83)	-0.09 (-0.26, 0.09)	
	HK/19	28	304	1.90 (± 2.02)	1.65 (± 2.04)	-0.21 (-0.59, 0.18)	
	Tas/20	42	525	3.17 (± 2.97)	1.77 (± 2.11)	-0.63 (-0.95, -0.31)	

¹Total number of HAI assays across all assay strains and seasons.

²Fold change (post-vaccination titer divided by pre-vaccination titer. Geometric mean (\pm geometric standard deviation).

³Standardized mean difference (HD - SD); SMD (95% CI).

Seroprotection

Table 11 shows the crude analysis for the seroprotection outcome. The results were consistent with our main analysis, as well as the crude analyses of the other outcomes.

Table 11: Crude analysis of the seroprotection rate, stratified by dose.

Subtype	Vaccine strain	n ¹		Seroprotection ²		SMD ³
		SD	HD	SD	HD	
Overall	Overall	6,668	9,360	2822 (42%)	4533 (48%)	0.12 (0.09, 0.15)
H1N1	Overall	3,082	4,288	998 (32%)	1638 (38%)	0.12 (0.08, 0.17)
	CA/09	2,453	2,942	847 (35%)	1116 (38%)	0.07 (0.02, 0.12)
	MI/15	451	328	88 (20%)	117 (36%)	0.37 (0.22, 0.51)
	Bris/18	126	414	36 (29%)	117 (28%)	-0.01 (-0.21, 0.19)
	GD/19	28	304	10 (36%)	133 (44%)	0.16 (-0.22, 0.55)
	Vic/19	24	300	17 (71%)	155 (52%)	-0.40 (-0.82, 0.02)
H3N2	Overall	3,586	5,072	1824 (51%)	2895 (57%)	0.12 (0.08, 0.17)
	TX/12	1,544	972	733 (47%)	599 (62%)	0.29 (0.21, 0.37)
	Switz/13	720	1,042	378 (52%)	616 (59%)	0.13 (0.04, 0.23)
	HK/14	974	1,597	471 (48%)	904 (57%)	0.17 (0.09, 0.25)
	Sing/16	110	80	72 (65%)	46 (57%)	-0.16 (-0.45, 0.12)
	KS/17	168	552	118 (70%)	318 (58%)	-0.27 (-0.44, -0.09)
	HK/19	28	304	21 (75%)	166 (55%)	-0.44 (-0.83, -0.05)
	Tas/20	42	525	31 (74%)	246 (47%)	-0.57 (-0.89, -0.26)

¹Total number of HAI assays across all assay strains and seasons.

²Seroprotection (indicator for post-titer $\geq 1:40$); n (%).

³Standardized mean difference (HD - SD); SMD (95% CI).

Seroconversion

Table 12 shows the crude analysis for the seroconversion outcome. The results were consistent with our main analysis, as well as the crude analyses of the other outcomes. Notably, some of the vaccines have a much lower rate of seroconversion than seroprotection, and the SMDs for seroconversion between the two groups are quite negative, which is affected by both the smaller sample size in those groups as well as the higher pre-vaccination titers in the HD group.

Table 12: Crude analysis of the seroconversion rate, stratified by dose.

Subtype	Vaccine strain	n ¹		Seroconversion ²		
		SD	HD	SD	HD	SMD ³
Overall	Overall	6,668	9,360	981 (15%)	1710 (18%)	0.10 (0.06, 0.13)
H1N1	Overall	3,082	4,288	267 (09%)	535 (12%)	0.12 (0.08, 0.17)
	CA/09	2,453	2,942	203 (08%)	282 (10%)	0.05 (-0.01, 0.10)
	MI/15	451	328	19 (04%)	25 (08%)	0.14 (0.00, 0.29)
	Bris/18	126	414	23 (18%)	65 (16%)	-0.07 (-0.27, 0.13)
	GD/19	28	304	6 (21%)	62 (20%)	-0.03 (-0.41, 0.36)
	Vic/19	24	300	16 (67%)	101 (34%)	-0.70 (-1.12, -0.28)
H3N2	Overall	3,586	5,072	714 (20%)	1175 (23%)	0.08 (0.04, 0.12)
	TX/12	1,544	972	206 (13%)	211 (22%)	0.22 (0.14, 0.30)
	Switz/13	720	1,042	240 (33%)	378 (36%)	0.06 (-0.03, 0.16)
	HK/14	974	1,597	155 (16%)	276 (17%)	0.04 (-0.04, 0.12)
	Sing/16	110	80	13 (12%)	6 (08%)	-0.15 (-0.43, 0.14)
	KS/17	168	552	69 (41%)	191 (35%)	-0.13 (-0.31, 0.04)
	HK/19	28	304	8 (29%)	36 (12%)	-0.43 (-0.81, -0.04)
	Tas/20	42	525	23 (55%)	77 (15%)	-0.93 (-1.25, -0.61)

¹Total number of HAI assays across all assay strains and seasons.

²Seroconversion (indicator for post-titer $\geq 1:40$ only after vaccination); n (%).

³Standardized mean difference (HD - SD); SMD (95% CI).

Model diagnostics

We assessed model convergence and sampling using the \hat{R} statistic and the effective sample size (ESS) of the parameters. Detailed explanations of these metrics can be found in other sources [e.g. 15]. Briefly, \hat{R} assesses the mixing of the chains, and a large value indicates that chains have explored separate regions of the posterior or do not agree about the posterior density. The bulk ESS and tail ESS are two measures of the ESS, which provide information about how many draws of the parameters we would have if all of our draws were completely

uncorrelated (typically draws from the posterior are correlated and thus have less information than independent draws)

Since each of the models contains hundreds of parameters, it is not feasible to display every trace plot and diagnostic statistic in the summary. Table 13 contains an abbreviated summary of the most important diagnostic criteria, which were well within acceptable bounds ($\hat{R} \lesssim 1.01$ and both ESS $\gtrsim 1000$ for all parameters). While there were a handful of divergent transitions, they were negligible compared to the total amount of samples.

Table 13: Summarized diagnostic criteria for each of the four Bayesian models we fit.

Model	Num. Divergences	min E-BFMI	min ESS (tail)	min ESS (bulk)	max R_hat
Titer increase	7 / 20000	0.552	2808	1623	1.009
Post-vaccination titer	6 / 20000	0.587	3969	1848	1.011
Seroprotection	3 / 20000	0.571	1088	1148	1.009
Seroconversion	9 / 20000	0.565	4131	1979	1.008

Homologous model results

In the main text, we briefly mentioned that results which compared only the homologous vaccine response supported a positive effect of the HD vaccine compared to the SD vaccine, as shown in previous literature. Figure 2 shows our results when considering only the homologous response to each vaccine.

The credible intervals are wide, consistent with our other findings and in general with this type of complex observational data. However, all of the point estimates are positive, which matches previous literature on the effect of the HD vaccine on the homologous response.

Model results for other outcomes

While we think that modeling titer increase most directly answers our research question of interest (namely, whether the HD vaccine induces a stronger heterologous immune response than the SD vaccine), titer increase is not the only outcome with clinical interest. We also fit models with post-vaccination titer, seroprotection, and seroconversion as the outcomes, detailed in the previous sections on model fitting. Here, we show the three figures from our main results, but using the alternative model outcomes.

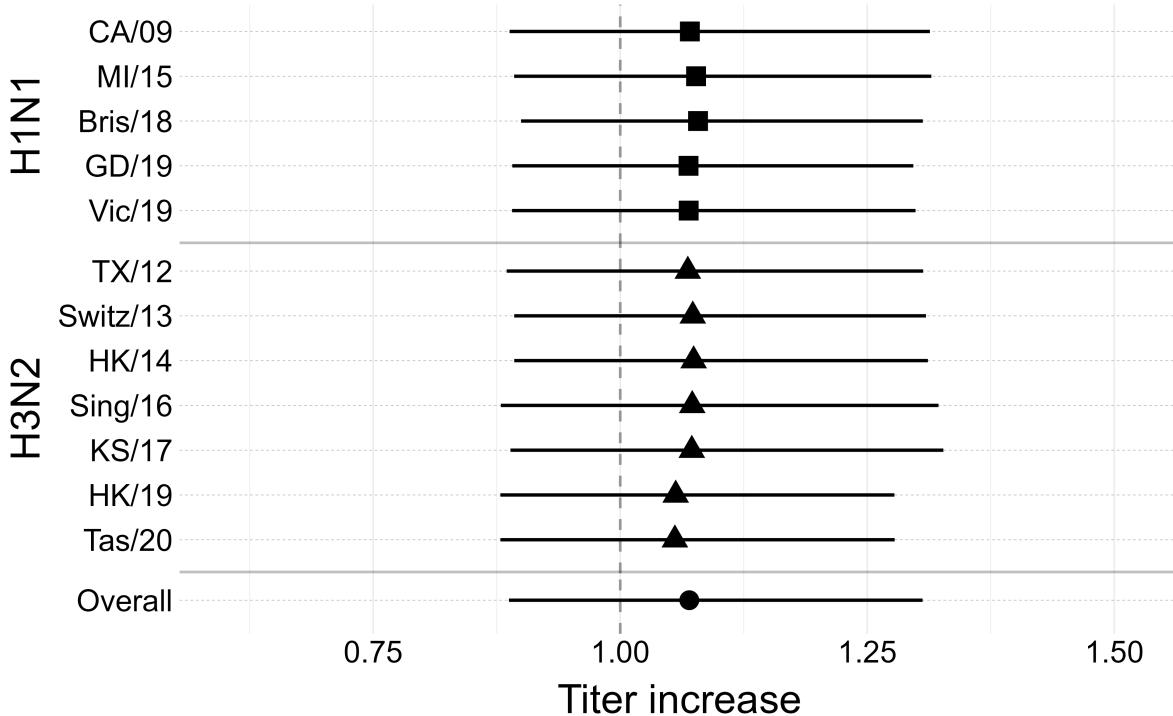


Figure 2: Exponentiated cACE estimates for each vaccine strain and overall. Only homologous responses to each vaccine were considered.

Post-vaccination titer

All of the figures in this section show the results for post-vaccination titer as the model outcome. All of our results agreed with the results in the main text and there were no major qualitative differences.

Figure 3 shows the cACEs for each vaccine strain when only the heterologous strains were included.

Figure 4 shows the cACEs for all assay strains.

Figure 5 shows the cACEs for all vaccine strains, pooling assay strains together within each vaccine strain.

Figure 6 shows the cACEs for each season, with the vaccine strain and assay strains for that season all pooled together.

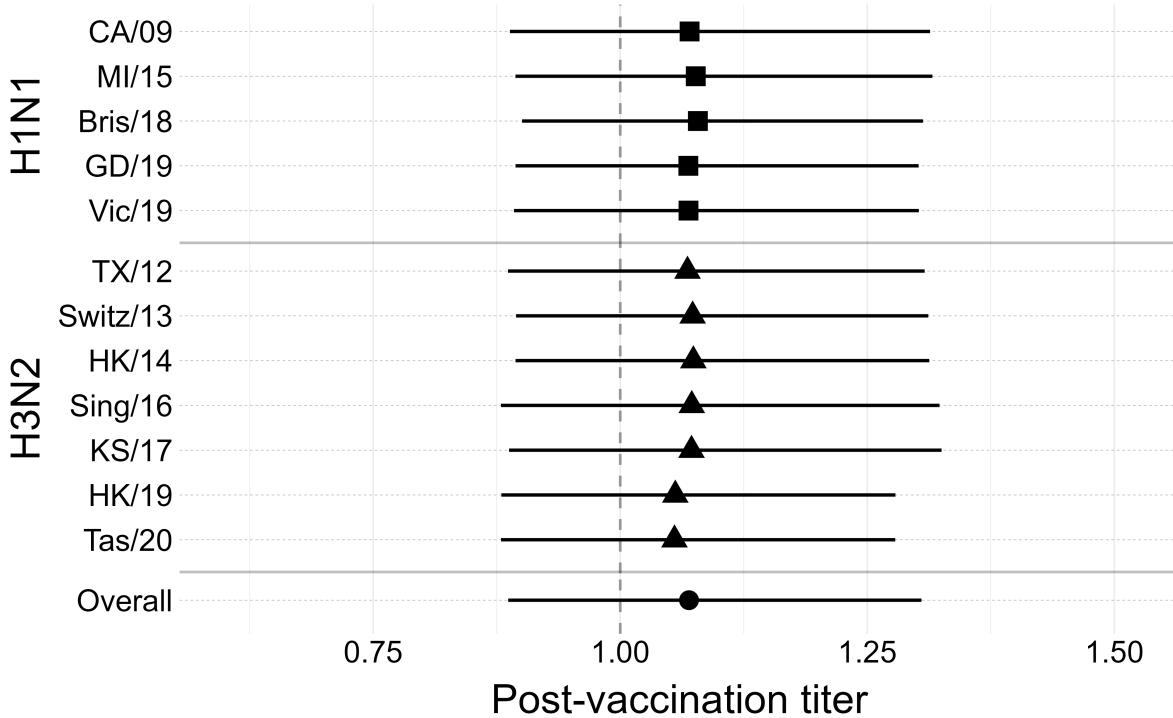


Figure 3: Exponentiated ACE estimates for each vaccine strain and overall. Only homologous responses to each vaccine were considered.

Seroprotection

All of the figures in this section show the results for seroprotection as the model outcome. All of our results agreed with the results in the main text and there were no major qualitative differences.

Figure 7 shows the cACEs for each vaccine strain when only the heterologous strains were included.

Figure 8 shows the cACEs for all assay strains.

Figure 9 shows the cACEs for all vaccine strains, pooling assay strains together within each vaccine strain.

Figure 10 shows the cACEs for each season, with the vaccine strain and assay strains for that season all pooled together.

Seroconversion

All of the figures in this section show the results for seroconversion as the model outcome. All of our results agreed with the results in the main text and there were no major qualitative differences.

Figure 11 shows the cACEs for each vaccine strain when only the heterologous strains were included.

Figure 12 shows the cACEs for all assay strains.

Figure 13 shows the cACEs for all vaccine strains, pooling assay strains together within each vaccine strain.

Figure 14 shows the cACEs for each season, with the vaccine strain and assay strains for that season all pooled together.

Session information

The complete R session information for all of our required packages is shown here.

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Finding R package dependencies ... Done!

R version 4.4.1 (2024-06-14 ucrt)
Platform: x86_64-w64-mingw32/x64
Running under: Windows 10 x64 (build 19045)

Matrix products: default

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[2] LC_CTYPE=English_United States.utf8
[3] LC_MONETARY=English_United States.utf8
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time zone: America/New_York
tzcode source: internal

attached base packages:
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```

```
other attached packages:
```

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[1] flextable_0.9.6
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loaded via a namespace (and not attached):
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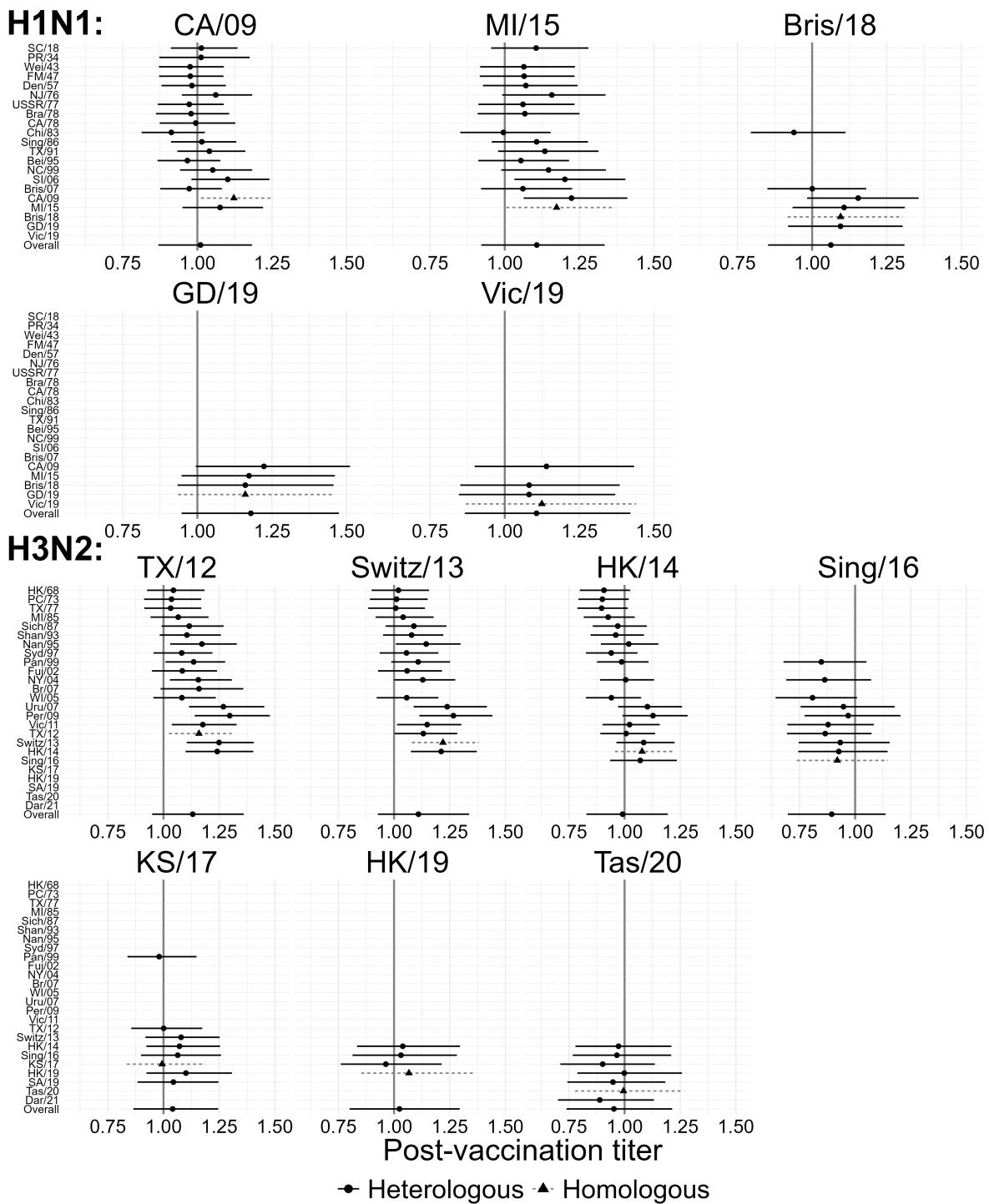


Figure 4: Exponentiated cACE estimates for each assay strain, within vaccine strains

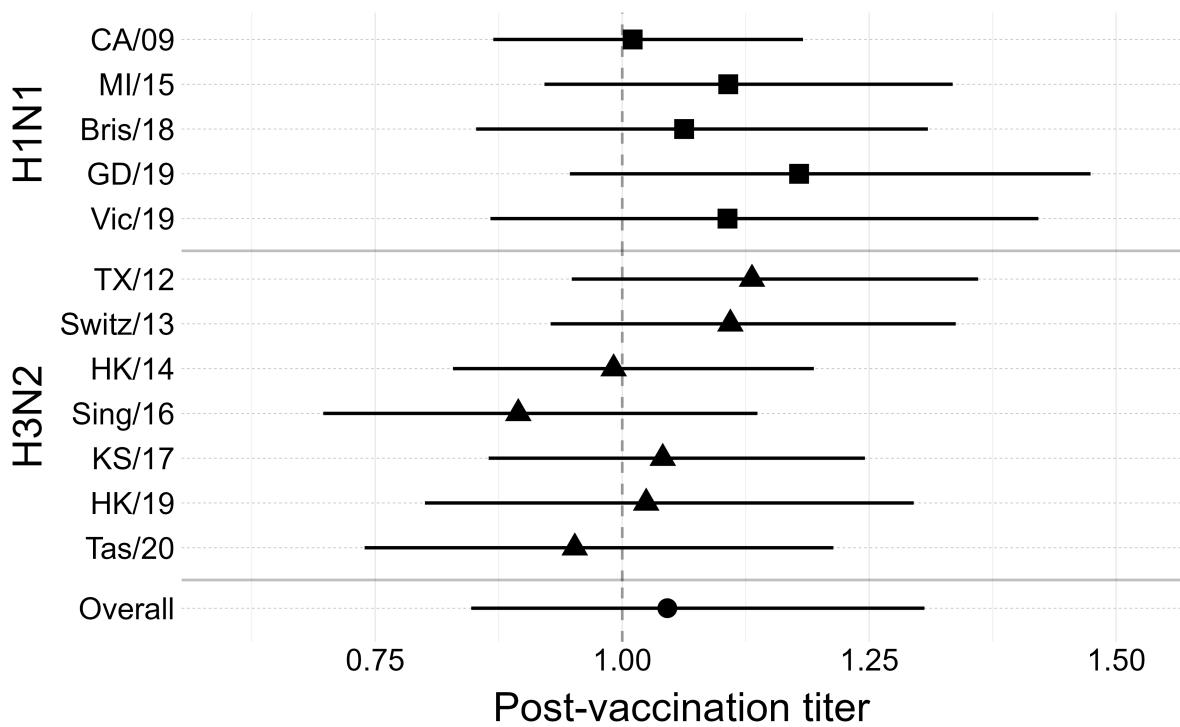


Figure 5: Exponentiated ACE estimates for each vaccine strain and overall.

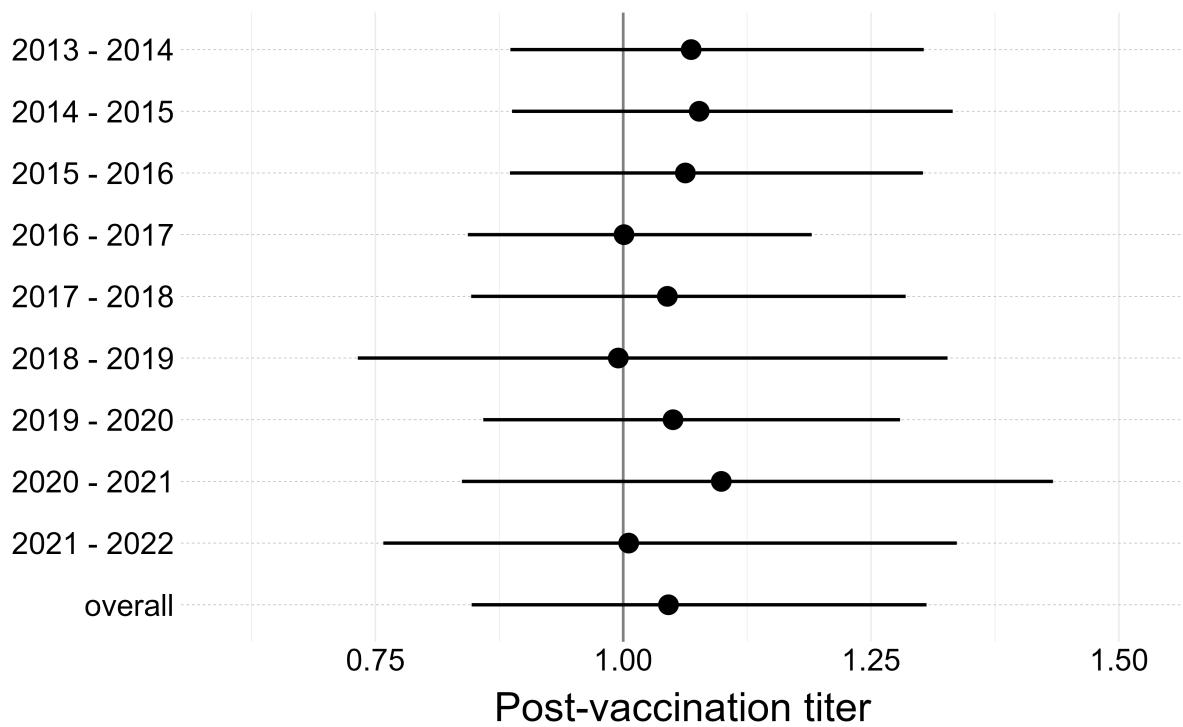


Figure 6: Exponentiated cACE for each season, over all vaccine strains and assay strains.

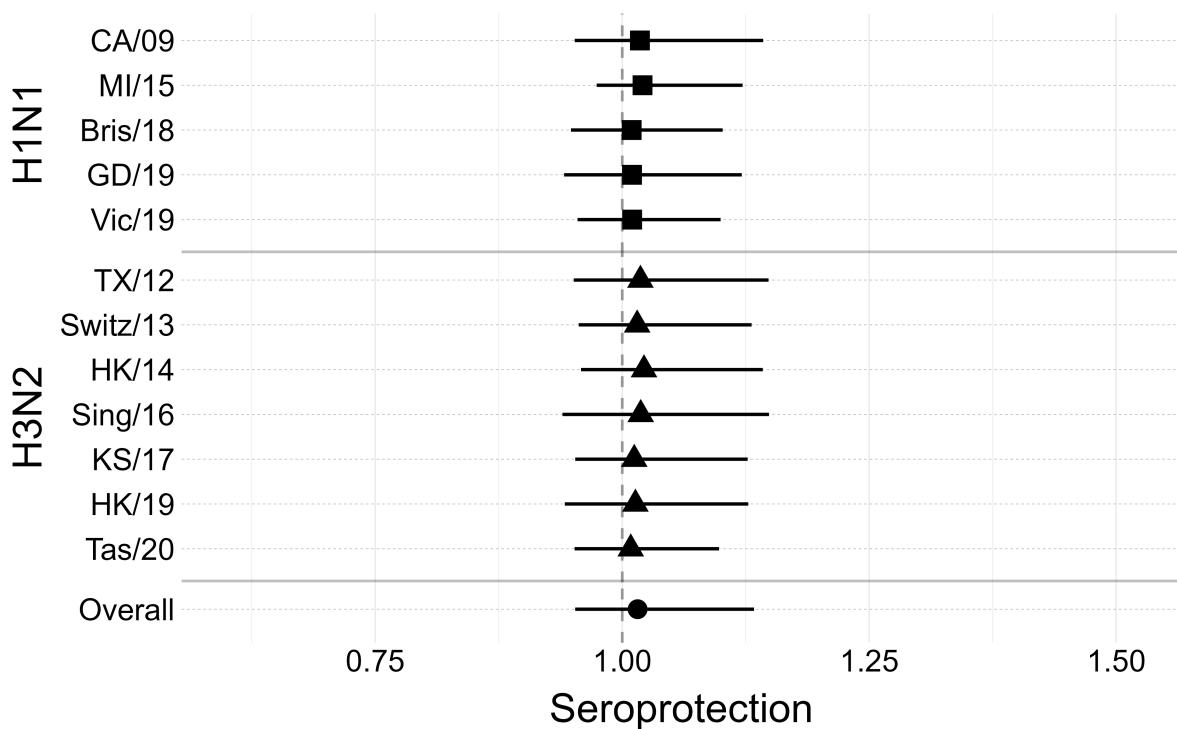


Figure 7: Exponentiated ACE estimates for each vaccine strain and overall. Only homologous responses to each vaccine were considered.

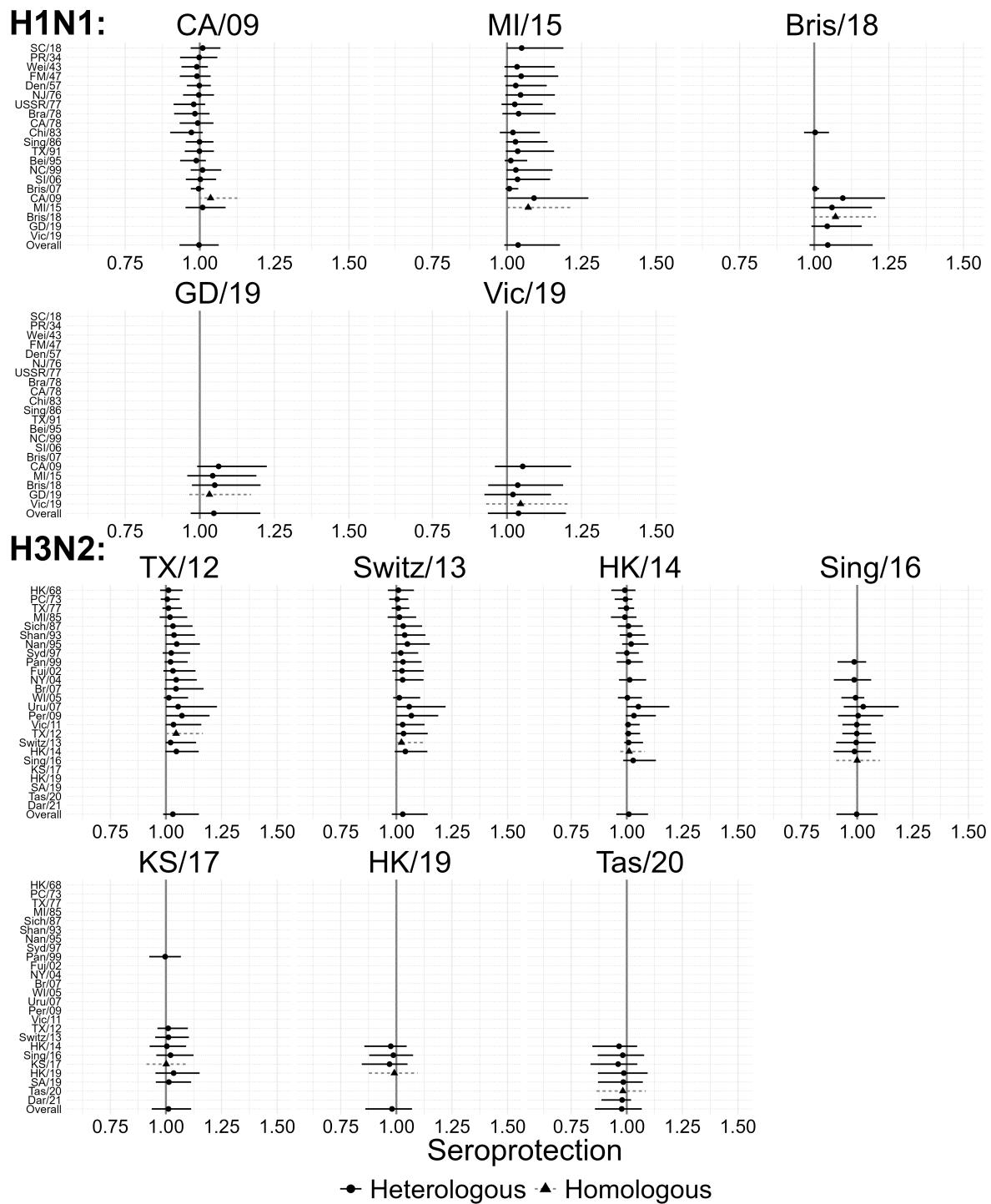


Figure 8: Exponentiated cACE estimates for each assay strain, within vaccine strains

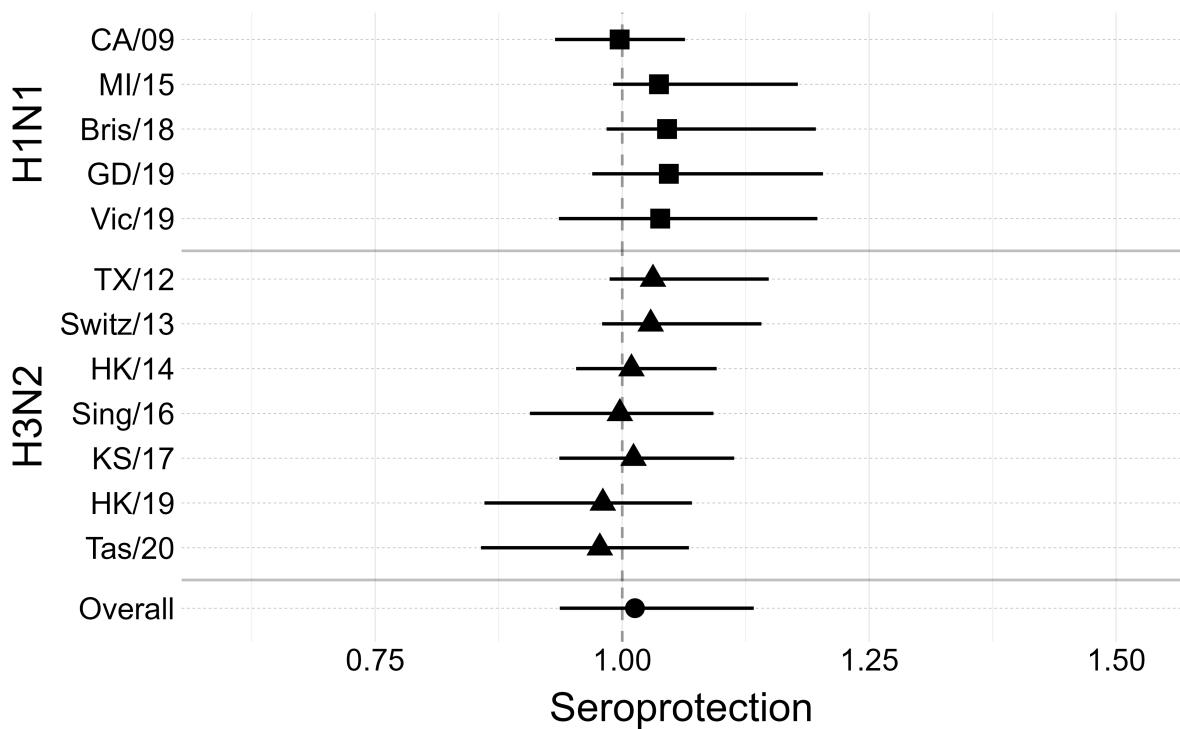


Figure 9: Exponentiated ACE estimates for each vaccine strain and overall.

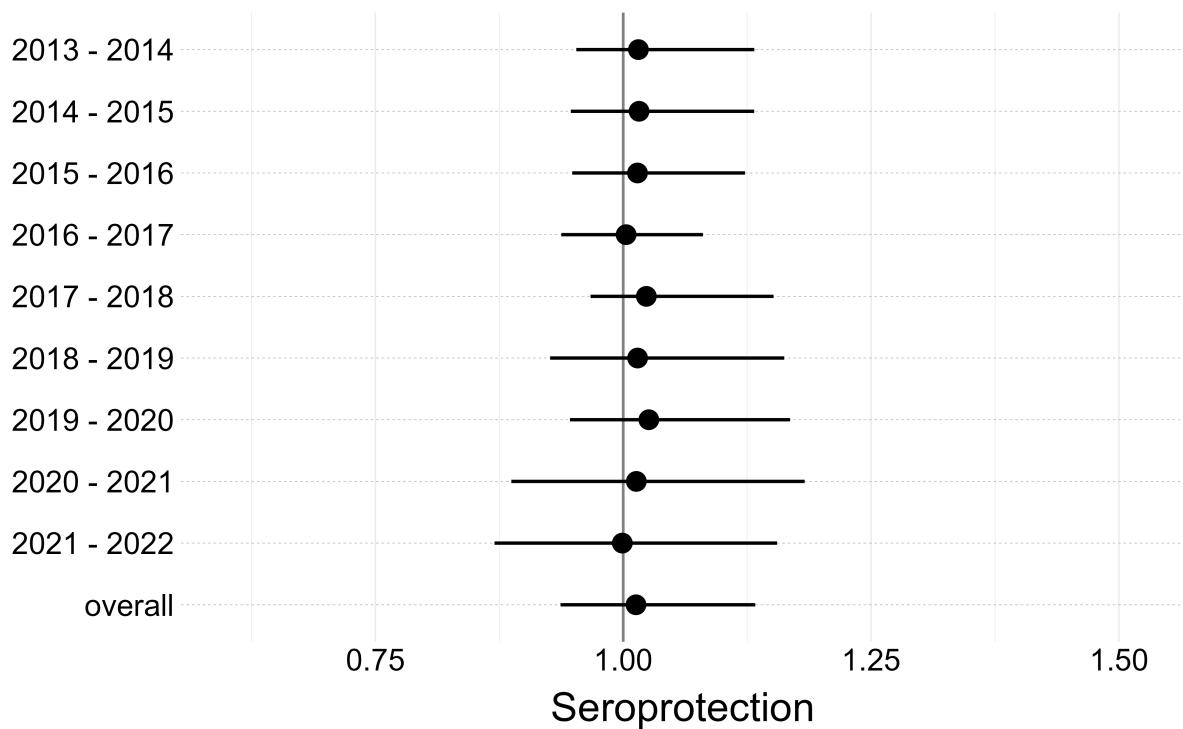


Figure 10: Exponentiated cACE for each season, over all vaccine strains and assay strains.

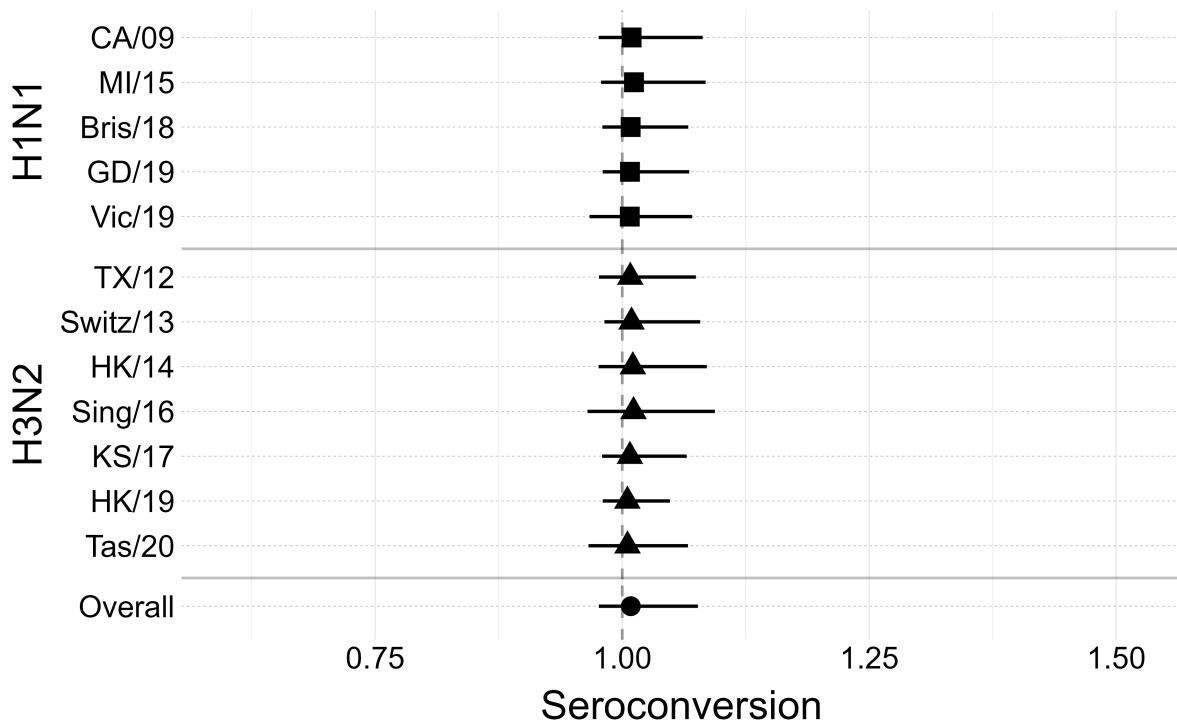


Figure 11: Exponentiated ACE estimates for each vaccine strain and overall. Only homologous responses to each vaccine were considered.

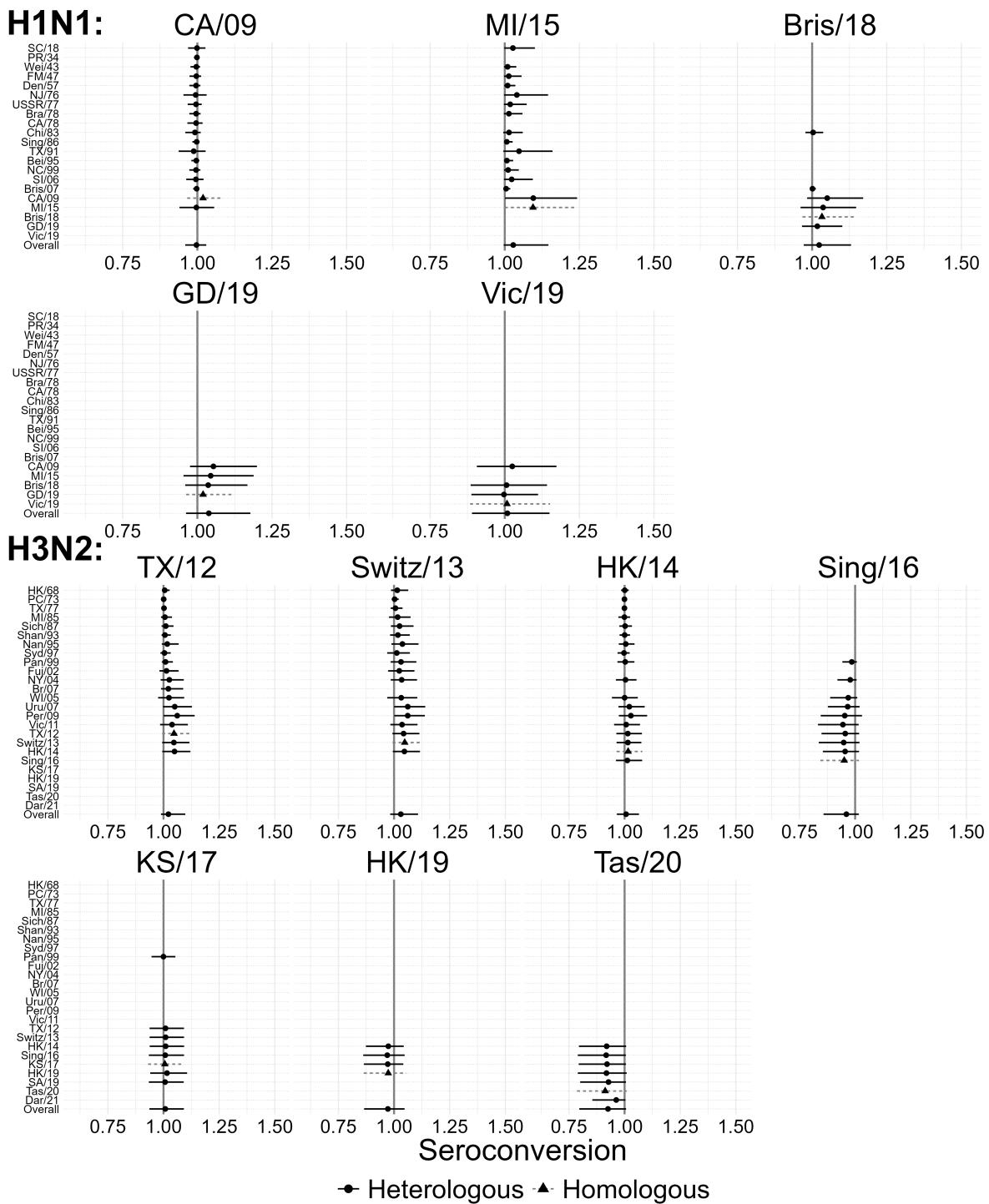


Figure 12: Exponentiated cACE estimates for each assay strain, within vaccine strains

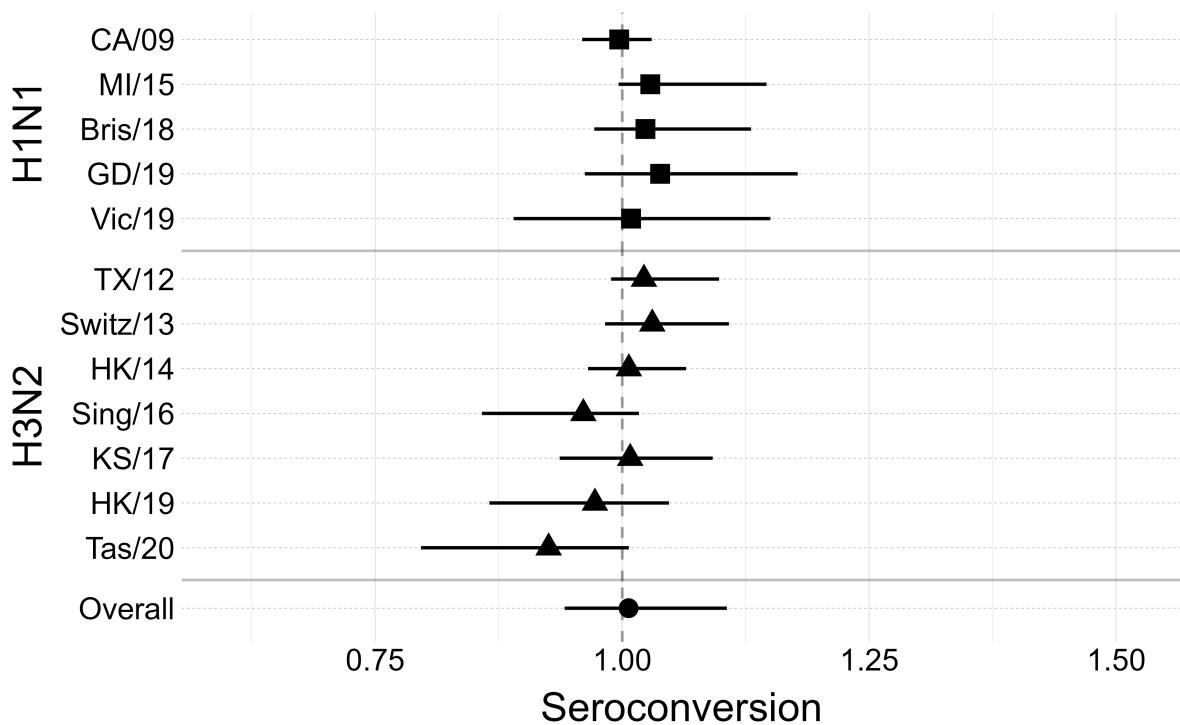


Figure 13: Exponentiated ACE estimates for each vaccine strain and overall.

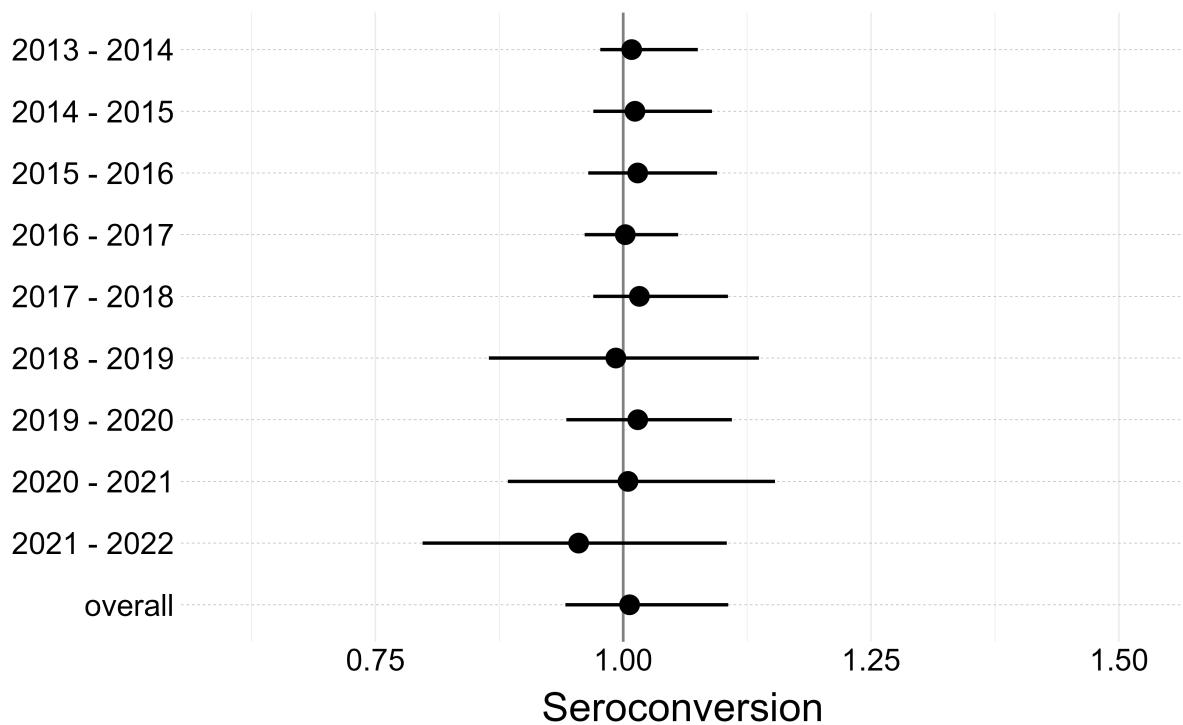


Figure 14: Exponentiated cACE for each season, over all vaccine strains and assay strains.

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