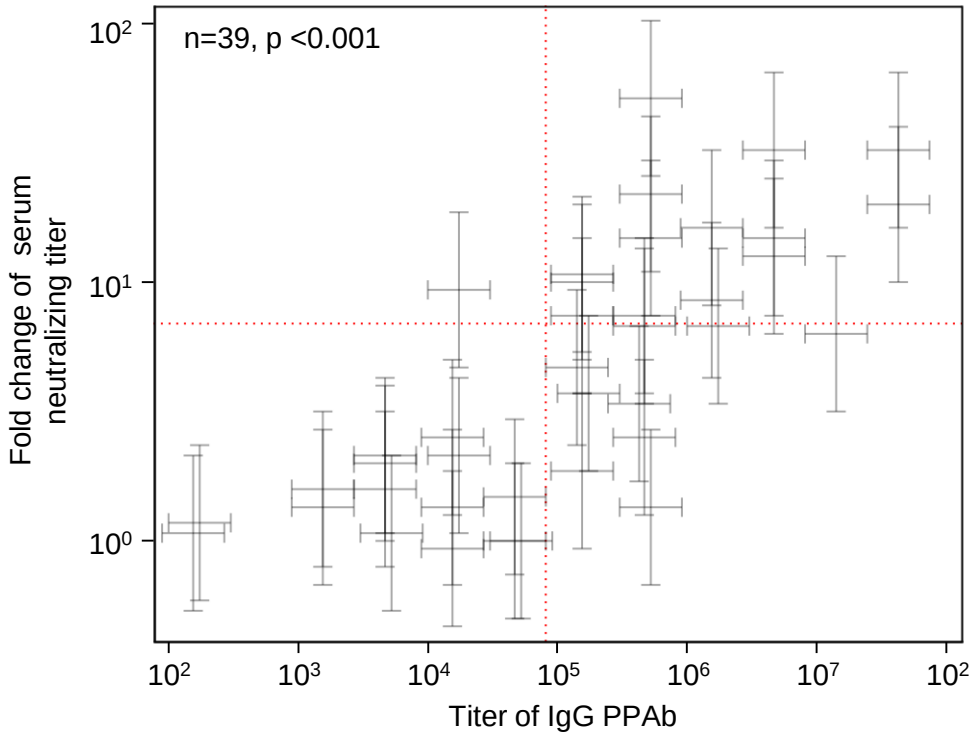
**Figure S1. Details of statistical method for Figure 1D.** Censored intervals were categorized as below, above or straddling the midpoint (red dotted line) for each variable, which generated a 3 × 3 contingency table of counts of observations. Using this contingency table, association between fold change of serum neutralizing titer and PPAb IgG (titer against 2011 TIV) was tested using a Freeman-Halton exact test [1].

**Reference:**

1. G. H. Freeman and J. H. Halton. Note on an exact treatment of contingency, goodness of fit and other problems of significance. Biometrika **1951**; 38:141-149.



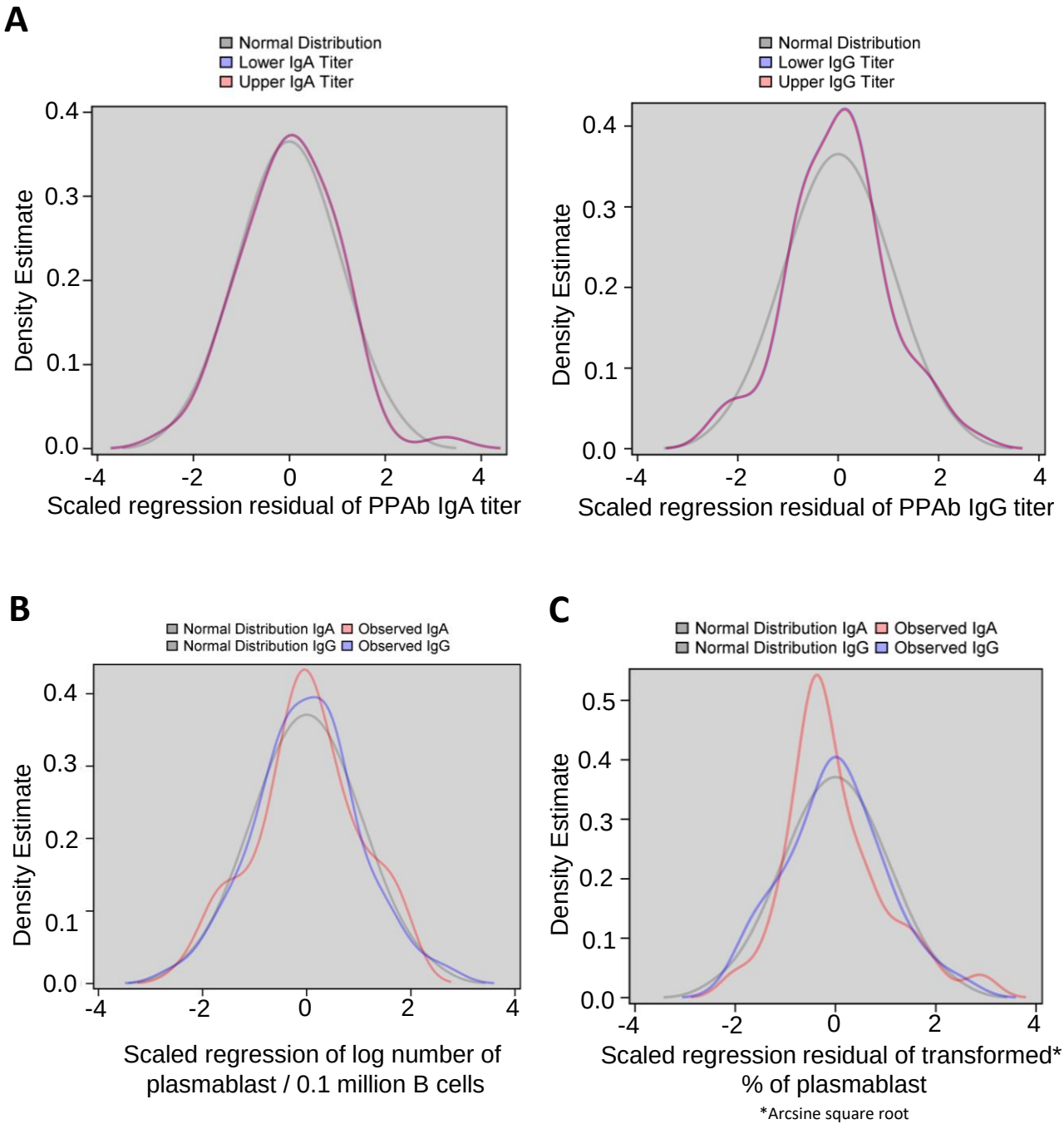
## Supplemental Figures

**Figures S2 – S5. Fit of shared-parameter model to longitudinal outcomes.** All figures compare the kernel density estimate [1] of the distribution of the observed data to the parametric distribution assumed for that model. Presented observed data are residuals (unexplained variation) from the fit of the regression model. Data were logarithm transformed prior to regression analysis for IgA PPAb and IgG PPAb titers (Figure S2A), numbers of IgA and IgG plasmablasts per $10^5$ B cells (Figure S2B), and fold change of HAI titer (Figure S4). Percentages of IgA and IgG plasmablasts (Figure S2C) were arcsine square root transformed [2] prior to analysis. To limit the effect of larger relative errors of the smaller AUC values on comparison between years (Figure 3), the HA-specific binding activity data were not transformed for results presented in main text (see also Figure S3). For comparison, results for transformed HA-specific binding activity data are shown in Figures S12 and S13.

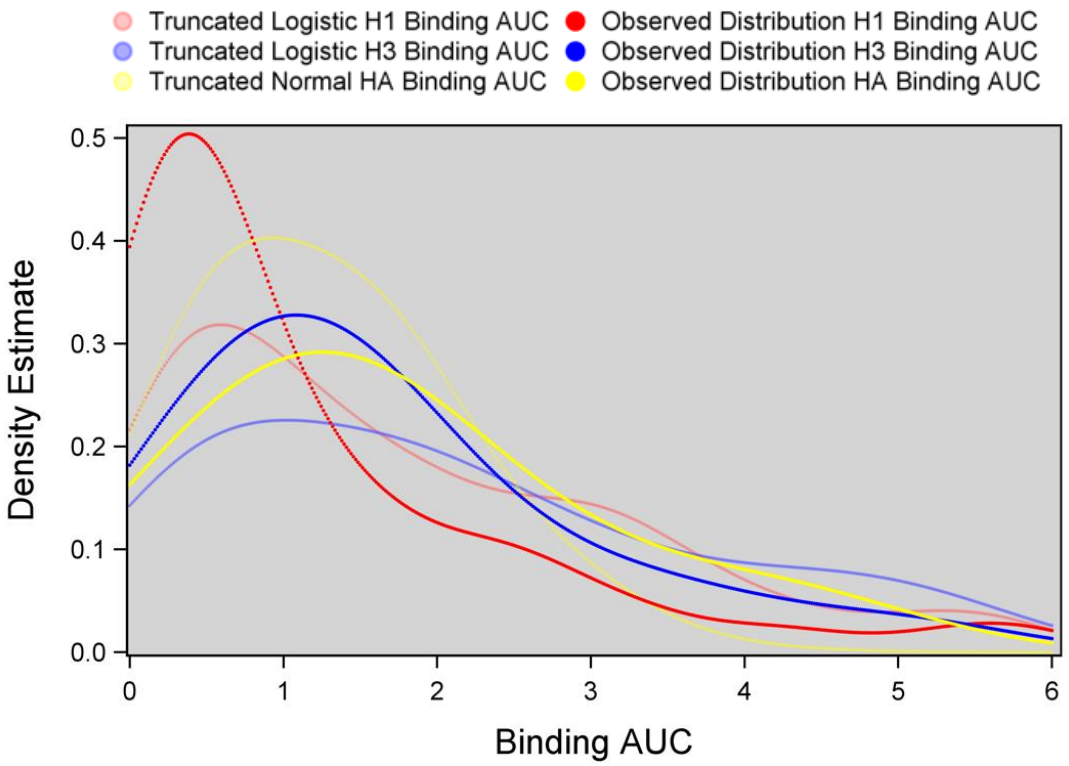
**References:**

1. Silverman BW. Density estimation for statistics and data analysis. London; New York: Chapman and Hall, **1986**.
2. Sokal RR. Biometry: the principles and practice of statistics in biological research. In: Rohlf FJ, ed. 2nd ed. San Francisco: W.H. Freeman, **1981**:427-8.

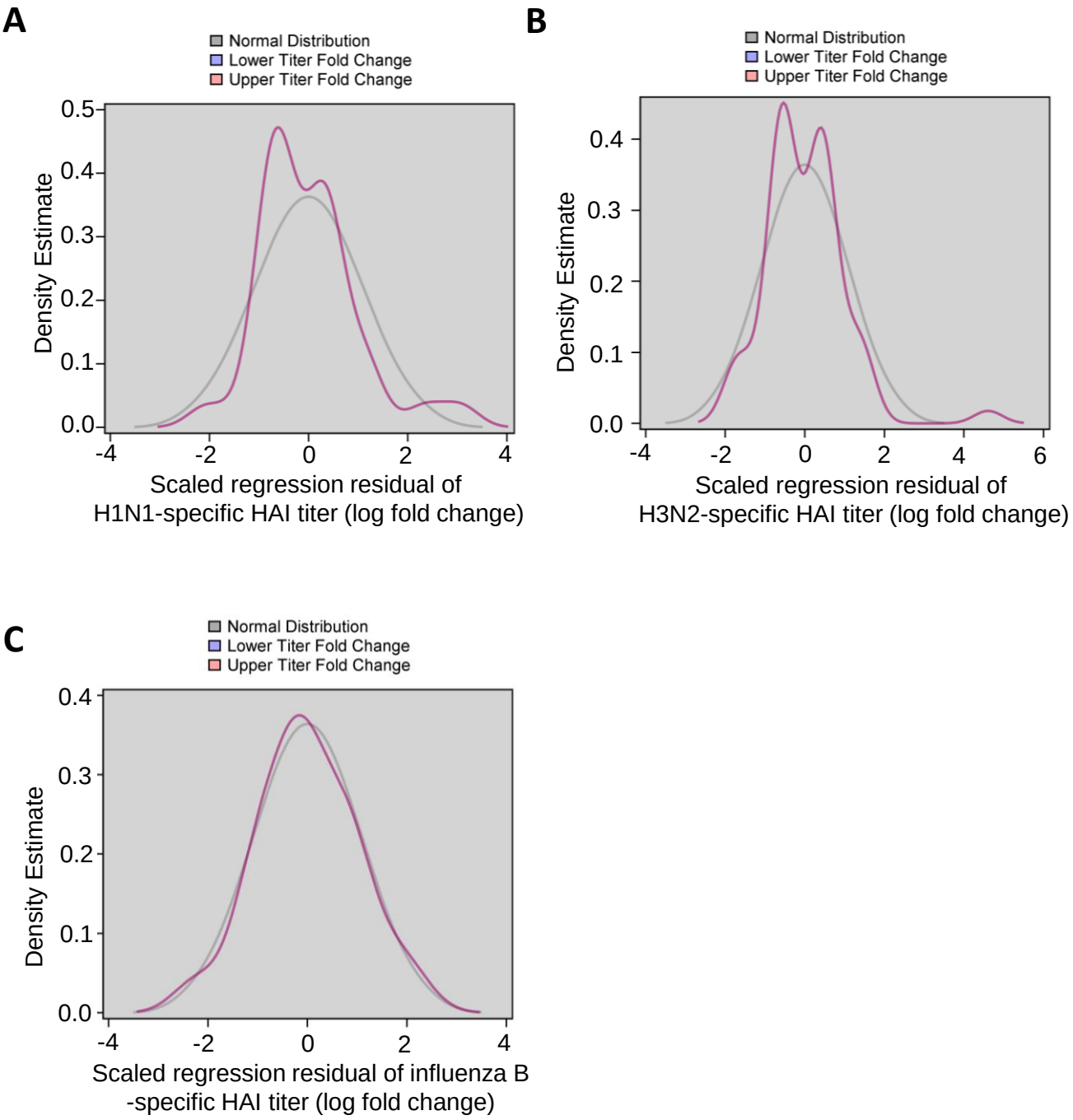
# Figure S2


A
Normal Distribution
Lower IgA Titer
Upper IgA Titer
Density Estimate
0.4
0.3
0.2
0.1
0.0
-4
-2
0
2
4
Scaled regression residual of PPAb IgA titer
Normal Distribution
Lower IgG Titer
Upper IgG Titer
Density Estimate
Scaled regression residual of PPAb IgG titer
B
Normal Distribution IgA
Observed IgA
Normal Distribution IgG
Observed IgG
Density Estimate
Scaled regression of log number of plasmablast / 0.1 million B cells
C
Normal Distribution IgA
Observed IgA
Normal Distribution IgG
Observed IgG
0.5
Density Estimate
Scaled regression residual of transformed* % of plasmablast
*Arcsine square root

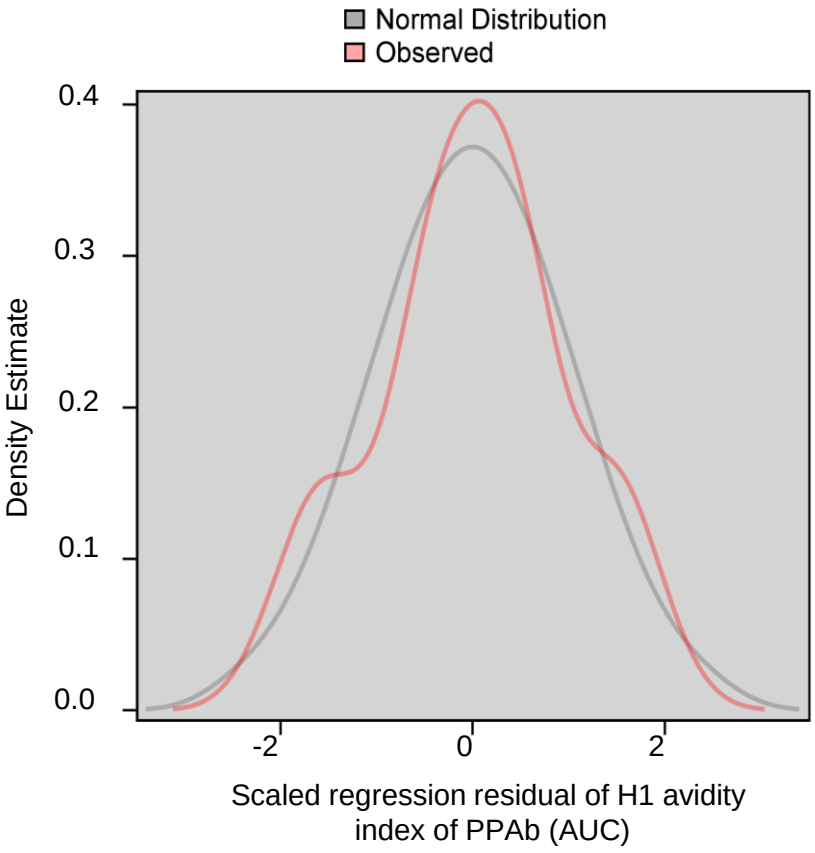
# Figure S3


Truncated Logistic H1 Binding AUC
Truncated Logistic H3 Binding AUC
Truncated Normal HA Binding AUC
Observed Distribution H1 Binding AUC
Observed Distribution H3 Binding AUC
Observed Distribution HA Binding AUC
Density Estimate
0.0
0.1
0.2
0.3
0.4
0.5
0
1
2
3
4
5
6
Binding AUC

# Figure S4


A
Normal Distribution
Lower Titer Fold Change
Upper Titer Fold Change
Density Estimate
0.5
0.4
0.3
0.2
0.1
0.0
-4
-2
0
2
4
Scaled regression residual of
H1N1-specific HAI titer (log fold change)
B
Normal Distribution
Lower Titer Fold Change
Upper Titer Fold Change
Density Estimate
0.4
0.3
0.2
0.1
0.0
-4
-2
0
2
4
6
Scaled regression residual of
H3N2-specific HAI titer (log fold change)
C
Normal Distribution
Lower Titer Fold Change
Upper Titer Fold Change
Density Estimate
0.4
0.3
0.2
0.1
0.0
-4
-2
0
2
4
Scaled regression residual of influenza B
-specific HAI titer (log fold change)

# Figure S5


Normal Distribution
Observed
Density Estimate
0.4
0.3
0.2
0.1
0.0
-2
0
2
Scaled regression residual of H1 avidity index of PPAb (AUC)

**Figures S6 – S9. Vaccine-specific B cell/antibody response in 2010/2011 is positively associated with participant duration on study.** The shared-parameter model permitted estimation of association between the 2010/2011 level of each outcome and participant duration on study (2010/2011 through 2014). This association was detected ($p < 0.05$) at various estimated strengths in the four outcomes shown (Figures S6 – S9). Positive association indicates that higher levels of immune response in 2010/2011 were associated with longer duration on study. Participants who leave the study in third or fourth year are estimated to have had lower levels of the immune response after their first vaccination. The shared-parameter model may at least partially correct [1] bias in estimates of 2013-2014 seasonal means due to any dropout that depends upon observed and unobserved (latent) baseline characteristics of the participant. In Figure 2A, the regression model's estimates of the means in 2013 and 2014 (black circles) sit low in the observed data indicating that the regression model is adjusting those means downward to account for low responders in 2010/2011 who dropped from the study.

Technical Note: We employed these shared-parameter regression models specifically because they could be applied to the range of longitudinal outcomes examined, including interval-censored longitudinal outcomes (titer and titer fold change). We appreciate that model assumptions can impact findings; so we were careful to examine the distributional assumptions of the longitudinal outcomes (Figures S2A through S5). Further, the fitting algorithm was supplied with a grid of starting values to ensure identification of the global optimum. To further assess robustness of findings, in separate analyses, we transformed HA-specific binding activity data prior to analysis (Figures S12 and S13). Finally, we employed a robust estimator of the covariance matrix of the parameter estimates [2] as an additional safeguard against departures from regression model assumptions.

**References:**

1. McCulloch CE. Joint modelling of mixed outcome types using latent variables. Statistical methods in medical research. **2016**; 17:53-73.

2. White H. Maximum. Likelihood Estimation of Misspecified Models. Econometrica **1982**; 50:1-25.

## Figure S6

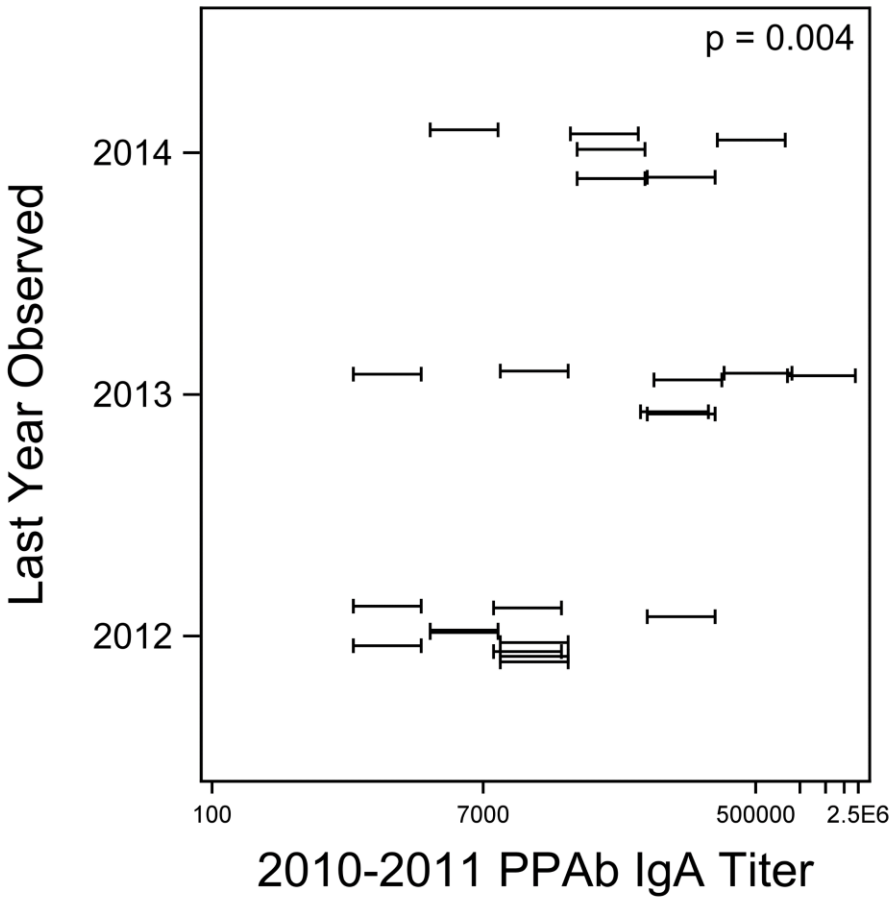
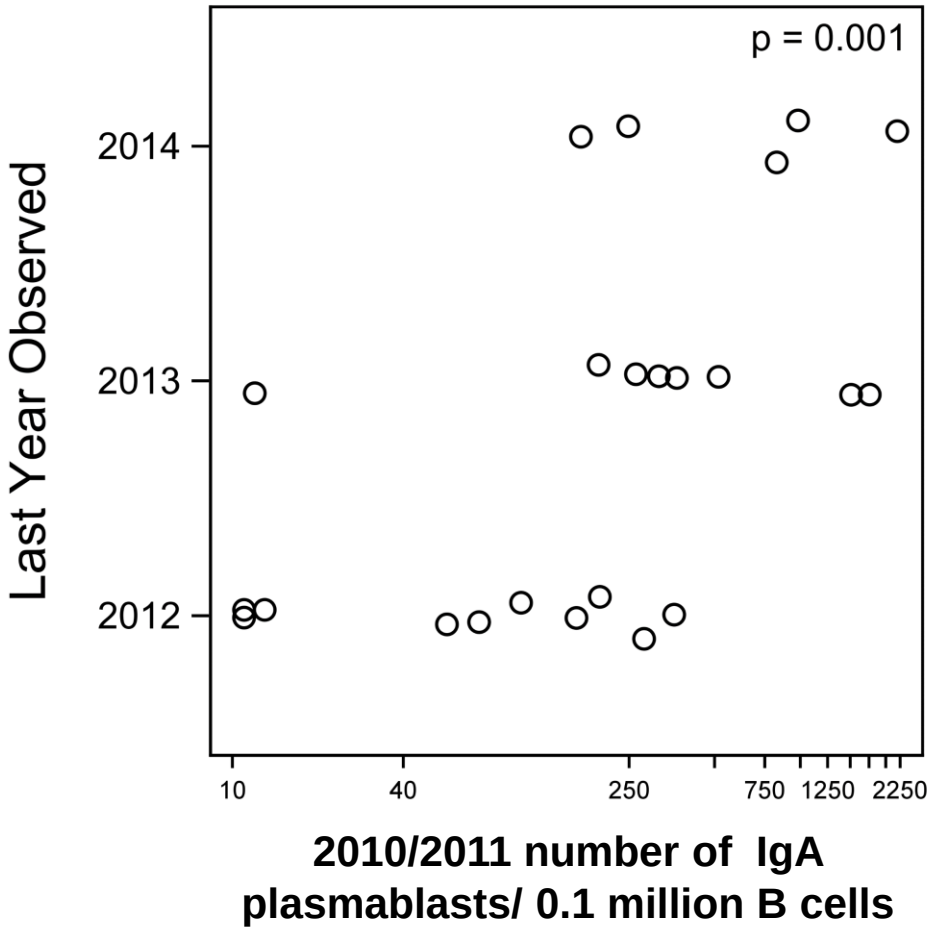
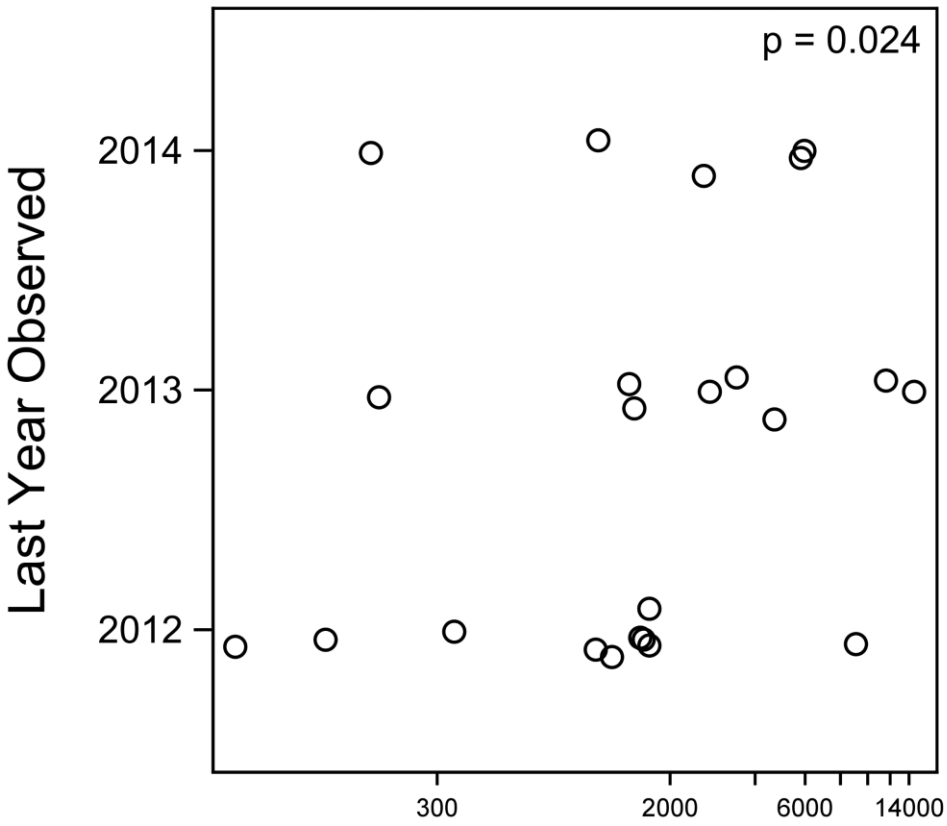

p = 0.004
Last Year Observed
2014
2013
2012
100
7000
500000
2.5E6
2010-2011 PPAb IgA Titer

**Figure S7**


p = 0.001
Last Year Observed
2014
2013
2012
10
40
250
750
1250
2250
2010/2011 number of IgA plasmablasts/ 0.1 million B cells

## Figure S8


p = 0.024
Last Year Observed
2014
2013
2012
300
2000
6000
14000
2010/2011 number of IgG plasmablasts/ 0.1 million B cells

## Figure S9

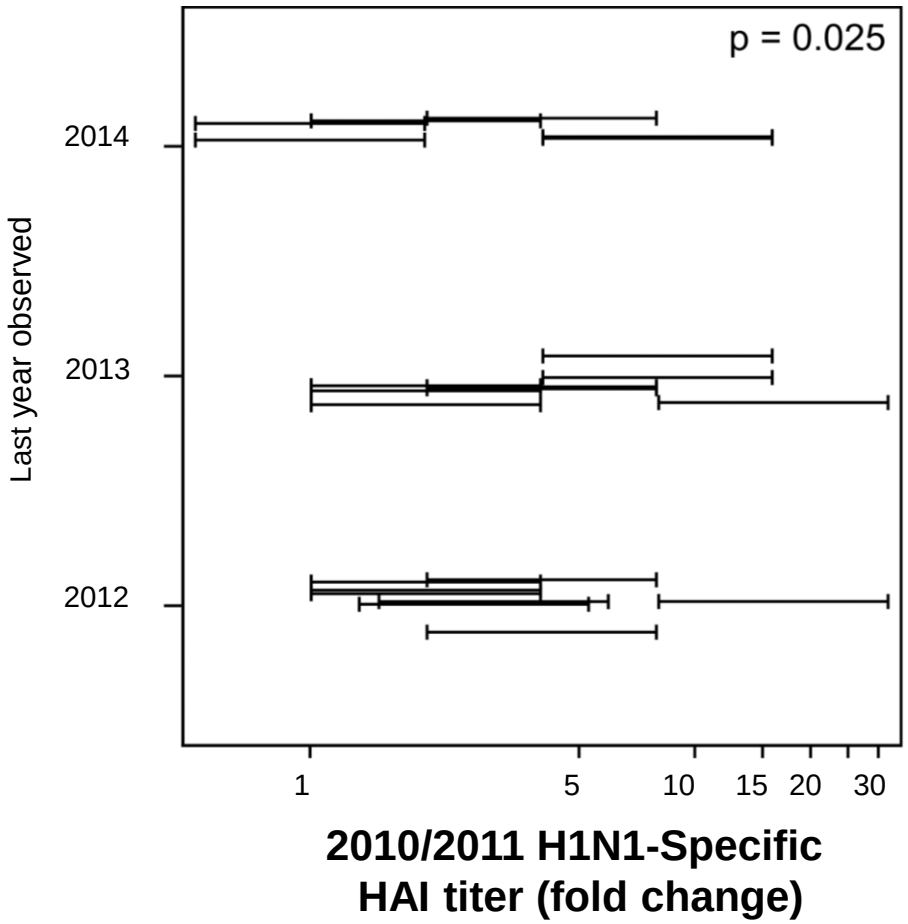

p = 0.025
2014
2013
2012
Last year observed
1
5
10
15
20
30
2010/2011 H1N1-Specific
HAI titer (fold change)

**Figure S10. Serum HAI titers before (day 0) and after (day 28) each TIV immunization. Titers were measured with 2x serially diluted samples. Each vertical bracket denotes the interval-censored titer. Data are randomly jittered in horizontal to facilitate viewing of individual titer intervals.**

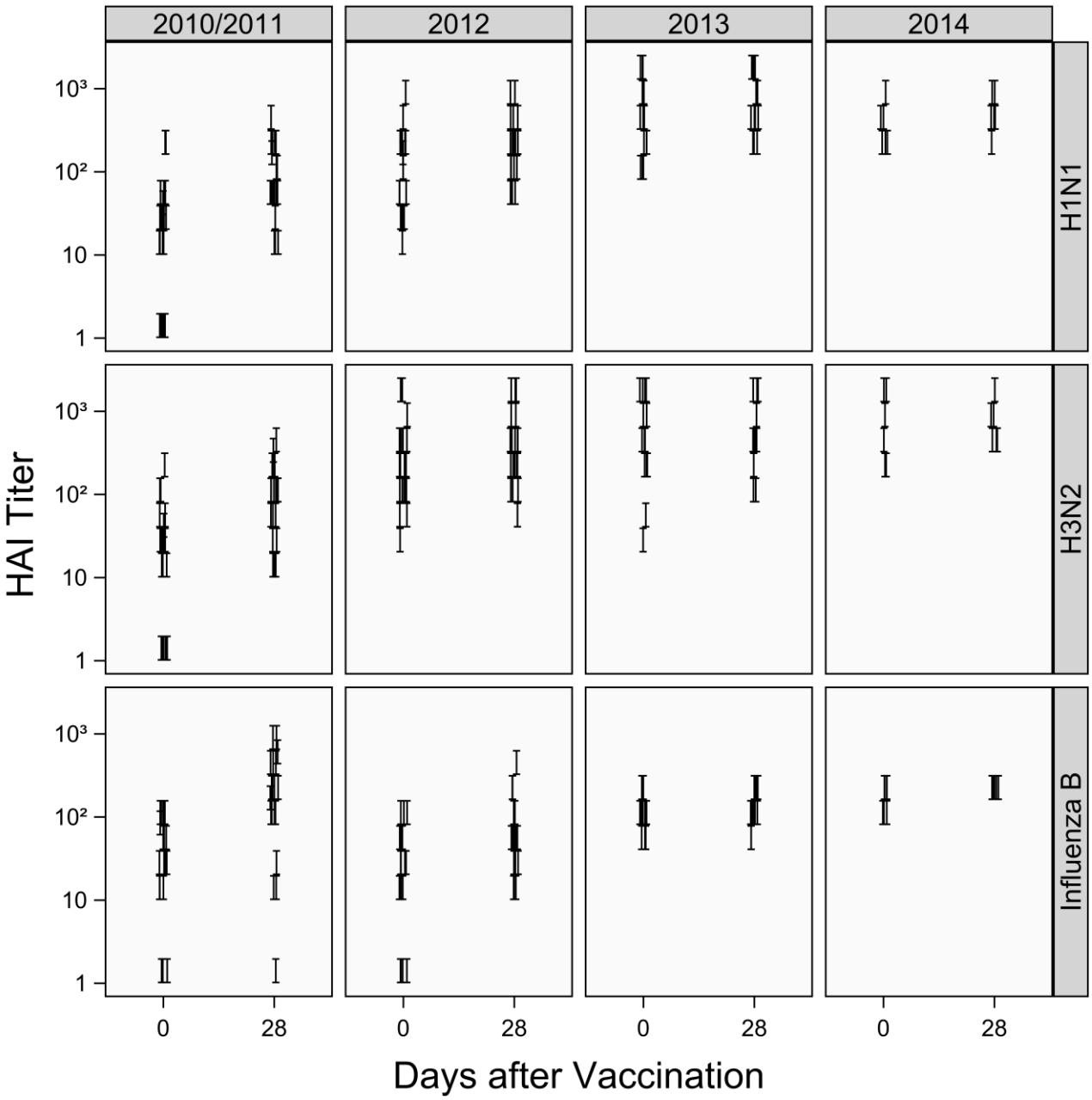
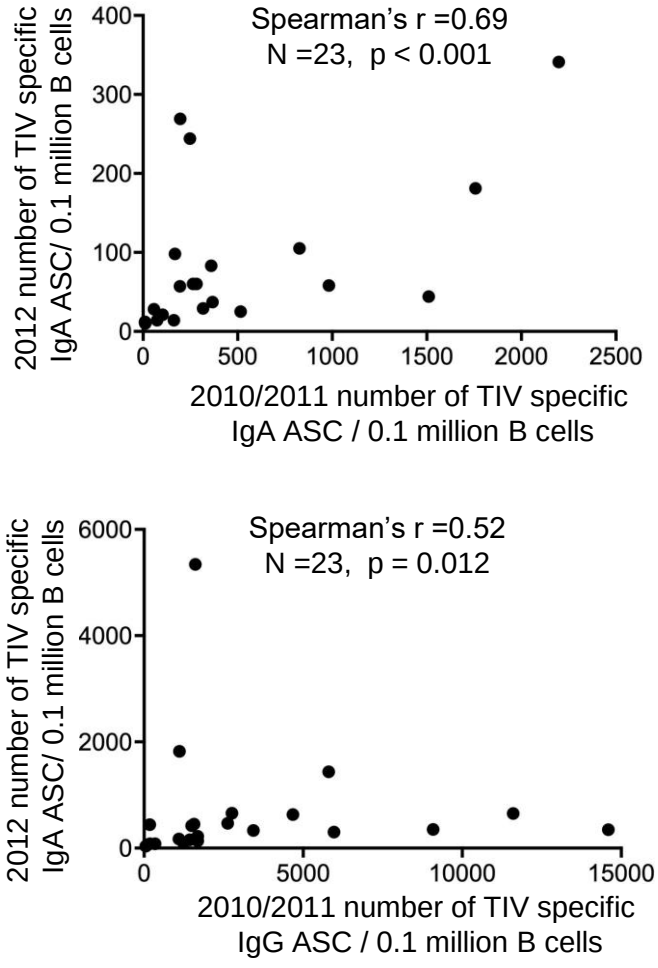


**Figure S11. Estimates of Spearman's correlation coefficient provide evidence of moderate association in vaccine-specific IgA and IgG plasmablast responses between 2010/2011 and 2012.**

# Figure S11



**Figures S12 – S13. Robustness Assessment: Results for transformed HA-specific binding activity data.** Logarithm (H3 and influenza B-HA) and square-root (H1) transformations were applied prior to shared-parameter regression analysis. Overall findings were similar to results for untransformed data shown in Figure 3. Compare untransformed data of Figures 3A – 3C of main text vs. transformed data of Figure S12. Fit of regression model is shown in Figure S13.

# Figure S12

| Marker | Means Comparison | Estimated Difference | Standard Error | P-value | P-value Adjusted for Multiple Comparisons |
|---|---|---|---|---|---|
| H1 Binding AUC | 2012 minus 2010/2011 | -0.6980 | 0.1473 | <.0001 | <.0001 |
| H1 Binding AUC | 2013 minus 2010/2011 | -0.9979 | 0.1187 | <.0001 | <.0001 |
| H1 Binding AUC | 2014 minus 2010/2011 | -0.7793 | 0.1614 | <.0001 | <.0001 |
| H1 Binding AUC | 2013 minus 2012 | -0.2999 | 0.1203 | 0.0173 | 0.0346 |
| H1 Binding AUC | 2014 minus 2013 | 0.2186 | 0.1454 | 0.1412 | 0.1412 |
| H3 Binding AUC | 2012 minus 2010/2011 | -0.3348 | 0.1097 | 0.0042 | 0.0210 |
| H3 Binding AUC | 2013 minus 2010/2011 | -0.2654 | 0.1310 | 0.0501 | 0.2004 |
| H3 Binding AUC | 2014 minus 2010/2011 | -0.3239 | 0.1950 | 0.1051 | 0.3153 |
| H3 Binding AUC | 2013 minus 2012 | 0.06942 | 0.1371 | 0.6155 | 1.0000 |
| H3 Binding AUC | 2014 minus 2013 | -0.05850 | 0.2260 | 0.7972 | 1.0000 |
| Influenza B HA Binding AUC | 2012 minus 2010/2011 | 0.1498 | 0.09156 | 0.1104 | 0.5520 |
| Influenza B HA Binding AUC | 2013 minus 2010/2011 | 0.08412 | 0.1177 | 0.4794 | 1.0000 |
| Influenza B HA Binding AUC | 2014 minus 2010/2011 | 0.1466 | 0.1301 | 0.2671 | 1.0000 |
| Influenza B HA Binding AUC | 2013 minus 2012 | -0.06564 | 0.09502 | 0.4940 | 1.0000 |
| Influenza B HA Binding AUC | 2014 minus 2013 | 0.06251 | 0.1355 | 0.6473 | 1.0000 |

## Figure S13

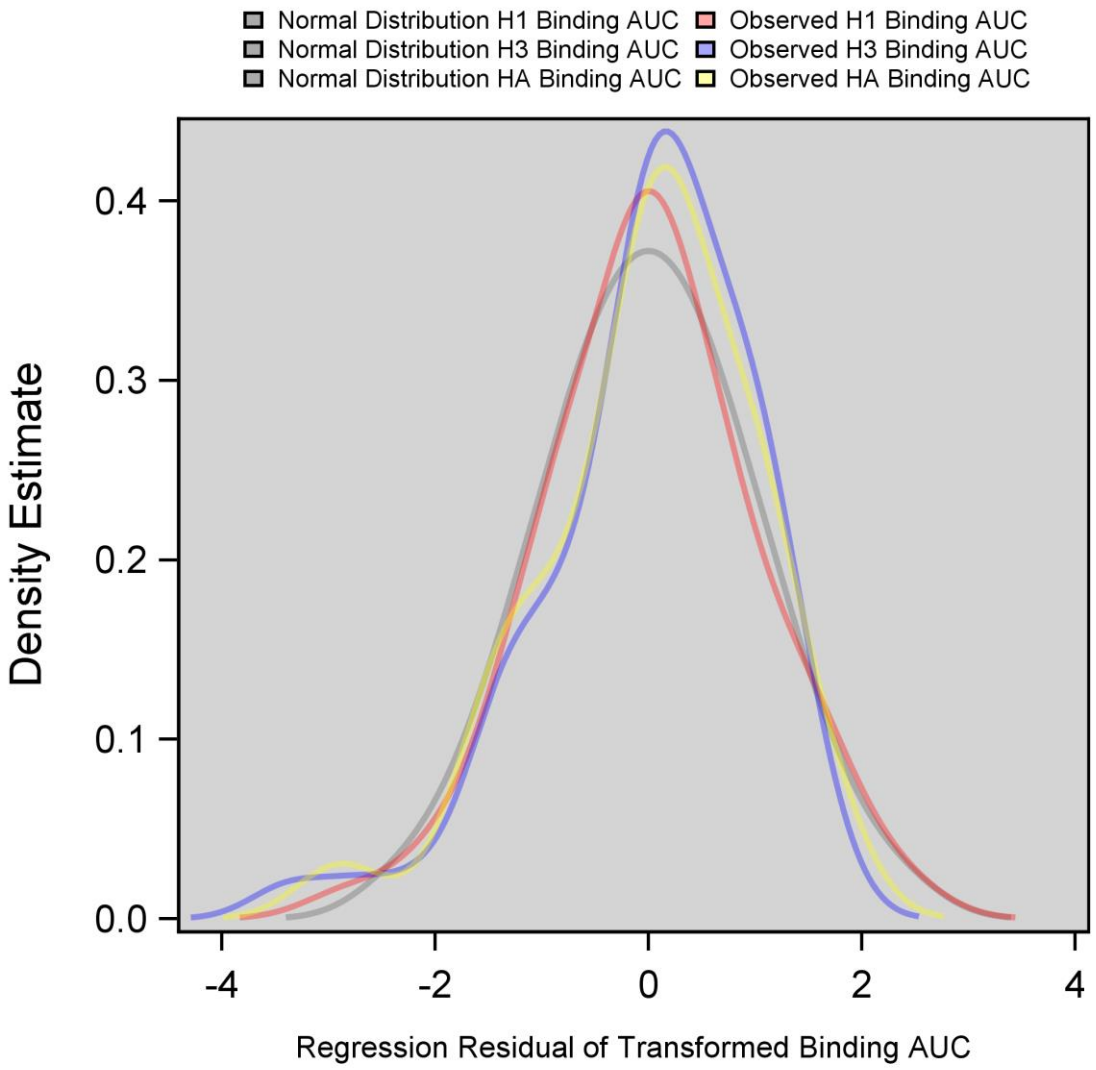

Normal Distribution H1 Binding AUC
Normal Distribution H3 Binding AUC
Normal Distribution HA Binding AUC
Observed H1 Binding AUC
Observed H3 Binding AUC
Observed HA Binding AUC
Density Estimate
0.0
0.1
0.2
0.3
0.4
-4
-2
0
2
4
Regression Residual of Transformed Binding AUC

**Figure S14. Example of possible regression to the mean illustrated for frequency of TIV-specific IgG ASC for all 62 participants.** (A) Frequencies of TIV-specific IgG ASC for those who did (Longitudinal) and did not (Baseline Only) re-enroll after baseline (2010/2011). Means of logarithm-transformed frequencies were compared between "Longitudinal" and "Baseline Only" groups using generalized maximum entropy estimation [1]. Because those who re-enroll (Longitudinal) appear to be enriched at baseline (2010/2011) with higher mean logarithmic frequencies of TIV-specific IgG ASC (p = 0.014), “regression to the mean" could be operating. (B) Approximate estimate of size of regression to the mean [2] is shown in shaded blue. Black lines connect observed values within each participant who re-enrolled after baseline (2010/2011). To estimate size of regression to the mean, within-person variance was calculated using the shared-parameter model described in the “Statistical Analyses” subsection of the main text and in legend to Online Supplement Figures S2 – S5.

**References:**

1. Golan, A., Judge, G. G., & Miller, D. (1996). Maximum entropy econometrics: Robust estimation with limited data. Chichester, England: Wiley.

2. Barnett, A. G., Van der Pols, J. C., & Dobson, A. J. (2005). Regression to the mean: what it is and how to deal with it. International Journal of Epidemiology 34: 215-220.

# Figure S14