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Serum per- and polyfluoroalkyl substance concentrations and longitudinal change in post-infection and post-vaccination SARS-CoV-2 antibodies

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Abstract

Per- and polyfluoroalkyl substances (PFAS) are ubiquitous throughout the United States. Previous studies have shown PFAS exposure to be associated with a reduced immune response. However, the relationship between serum PFAS and antibody levels following SARS-CoV-2 infection or COVID-19 vaccination has not been examined. We examined differences in peak immune response and the longitudinal decline of antibodies following SARS-CoV-2 infection and COVID-19 vaccination by serum PFAS levels in a cohort of essential workers in the United States. We measured serum antibodies using an in-house semi-quantitative enzyme-linked immunosorbent assay (ELISA). Two cohorts contributed blood samples following SARS-CoV-2 infection or COVID-19 vaccination. We used linear mixed regression models, adjusting for age, race/ethnicity, gender, presence of chronic conditions, location, and occupation, to estimate differences in immune response with respect to serum PFAS levels. Our study populations included 153 unvaccinated participants that contributed 316 blood draws over a 14-month period following infection, and 860 participants and 2451 blood draws over a 12-month period following vaccination. Higher perfluorooctane sulfonic acid (PFOS), perfluorohexane sulfonic acid (PFHxS), and perfluorononanoic acid (PFNA) concentrations were associated with a lower peak antibody response after infection (p=0.009, 0.031, 0.015). Higher PFOS, perfluorooctanoic acid (PFOA), PFHxS, and PFNA concentrations were associated with slower declines in antibodies over time after infection (p=0.003, 0.014, 0.026, 0.025). PFOA, PFOS, PFHxS, and PFNA serum concentrations prior to vaccination were not associated with differences in peak

antibody response after vaccination or with differences in decline of antibodies over time after vaccination. These results suggest that elevated PFAS may impede potential immune response to SARS-CoV-2 infection by blunting peak antibody levels following infection; the same finding was not observed for immune response to vaccination.

Keywords

Per- and polyfluoroalkyl substances (PFAS); COVID-19 vaccine; immune response; SARS CoV-2 infection; PFOS; PFOA

1. Introduction

Per- and polyfluoroalkyl substances (PFAS) are frequently found in the environment due to resistance to degradation and extensive use in industrial and consumer products (Lau et al., 2007). These predominantly man-made chemicals consist of over 9,000 different compounds (EPA, 2021) and are found in many products, including aqueous film forming foam (AFFF), stain-resistant surface treatment applications, cleaners, electronics, insulation, leather, lubricants, paper products, surfactants, and upholstery (Giesy and Kannan, 2002; Lewandowski et al., 2006). Based on nationally representative data from the National Health and Nutrition Examination Survey (NHANES), greater than 99% of NHANES participants age 12 and older have a detectable level of serum PFAS (Kato et al., 2011). Despite limited production in many countries, legacy PFAS, such as perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS), are still present in the environment today (Li et al., 2018). For the general population, in addition to ingestion of PFAS-contaminated food and drinking water, dermal absorption, indoor dust ingestion, and inhalation of ambient and indoor air can be important PFAS exposure pathways (DeLuca et al., 2022; Vestergren et al., 2008). Following absorption, PFAS can bioaccumulate in different tissues in the body, including the lung, heart, liver, blood, kidney, bone, skin, testis, and spleen (Bogdanska et al., 2020; Pérez et al., 2013). Some compounds have long (3 – 8.5 year) elimination half-lives (Olsen et al., 2007).

Multiple studies suggest a link between PFAS levels and immune response to pathogens or vaccination. The toxicological effects of PFAS on the immune system are thought to be caused by their ability to activate peroxisome proliferator-activated receptors (PPARs), causing an imbalance in cellular proinflammatory/anti-inflammatory modulation (Fang et al., 2008; Vanden Heuvel et al., 2006). Other proposed mechanisms include altered secretion of cytokines from antigen presenting cells (Ahuja et al., 2009), suppression of cytokines by immune cells through inhibition of NF-κB activation (Corsini et al., 2012), and increased B cell lymphocyte proliferation (Wirth et al., 2014). Additionally, increased concentrations of perfluorohexane sulfonic acid (PFHxS) and PFOS have been associated with altered lung surfactant function in human bronchoalveolar cells (Sørli et al., 2020).

To date most studies of immune response and PFAS have focused on children. Exposure to PFHxS in utero has been associated with increased risk of the total number of infections experienced during the first four years of life, with maternal exposure in the highest quartile associated with 1.5 times the odds of total infectious diseases in girls (Goudarzi et al.,

2017). Elevated serum concentrations of PFOS and PFOA in mothers have been associated with an increased duration of fever and co-occurrence of fever and cough or fever and nasal discharge in their children (Dalsager et al., 2016). In children, increased serum PFOS, PFOA, and PFHxS combined levels have been associated with reduced diphtheria and tetanus antibody levels from vaccination (Grandjean et al., 2012; Mogensen et al., 2015). In adolescents, increased PFOS levels have been associated with reduced rubella and mumps antibody levels (Stein et al., 2016).

There are far fewer studies among adults. In one study, increased serum PFAS concentrations, as measured by a number of analytes including PFOS and perfluorononanoic acid (PFNA), have been associated with a less robust increase in antibody levels after diphtheria and tetanus booster vaccinations (Kielsen et al., 2016). However, little is known about the effect of PFAS levels on antibody response to SARS-CoV-2 infection or COVID-19 vaccination despite the widespread prevalence of COVID-19. During the COVID-19 pandemic, researchers in Sweden and Italy demonstrated correlations between elevated PFAS levels and COVID-19 infection and mortality (Catelan et al., 2021; Nielsen and Jöud, 2021). A study using a case-control cohort from an area in China heavily polluted by PFAS found a statistically significant association between urinary levels of PFOA and summed PFOS (as measured by 12 common analytes) and SARS-CoV-2 infection (Ji et al., 2021). Another study found an association between increased plasma perfluorobutanoic acid (PFBA) levels and a more severe SARS-CoV-2 infection, but found no association for other common PFAS analytes (Grandjean et al., 2020). One other study involving pregnant individuals in New York City found a statistically significant relationship between increased maternal plasma PFAS concentrations and SARS CoV-2 anti-spike IgG antibody levels (Kaur et al., 2023). Two studies investigating the relationship between elevated PFAS exposure and antibody response to the COVID-19 vaccine found no statistically significant relationship (Bailey et al., 2023; Porter et al., 2022). These initial findings suggest that the relationships between individual PFAS serum concentrations and COVID-19 outcomes warrant further examination among the general population.

In this analysis, we explore the association between PFAS and SARS-CoV-2 infection immune response and PFAS and COVID-19 vaccination immune response in a cohort of first responders and frontline essential workers in the United States, a priority population in which to assess PFAS risk as these occupations are at increased risk of both PFAS exposure and COVID-19. First responders frequently have high occupational exposures to PFAS because PFAS compounds are found at 1 – 5% of the total composition in certain fire-suppression Class B aqueous film-forming foams (AFFF) and have been found to be present in fire response turnout-gear (Lewandowski et al., 2006; Vecitis et al., 2010). In addition, frontline workers, such as health care personnel and first responders, have increased risk of occupational exposure to SARS-CoV-2 (Shah et al., 2022). Within frontline workers, first responders, which includes correctional officers, fire fighters, law enforcement, and non-fire emergency medical services workers, are at increased risk for COVID-19 compared to health care workers, and this elevated risk has been observed to persist even after controlling for factors such as community transmission rates and frequency of mask use (Ellingson et al., 2021; Naleway et al., 2022).

We hypothesized that among frontline workers who were infected with SARS-CoV-2 before vaccines were widely available or who received a primary series of COVID-19 vaccination once available, higher serum PFAS concentrations are associated with lower immediate post-recovery and post-vaccination SARS-CoV-2 serologic antibody titers, as well as more rapid longitudinal decline in antibodies after initial recovery from infection or vaccination.

2. Materials and methods

Beginning in July 2020, frontline workers were followed in prospective cohorts through the Arizona Healthcare, Emergency Response, and Other Essential workers Study (AZ-HEROES) and the Research on the Epidemiology of SARS-CoV-2 in Essential Response Personnel (RECOVER) sites in Arizona, Florida, Minnesota, Oregon, Texas, and Utah. Details on these cohorts are described elsewhere (Edwards et al., 2021; Lutrick et al., 2021). Briefly, eligible participants included adults who worked at least 20 hours a week in occupations requiring frequent direct contact with others outside of their household during the pandemic. Upon enrollment, participants completed a survey to collect baseline information about sociodemographic and occupational characteristics, health status and behaviors, and prior SARS-CoV-2 infection. To determine SARS-CoV-2 infection prior to enrollment, participants were asked whether they had conducted any viral tests prior to enrollment, and whether any of these test results were positive. If yes, participants were then asked to give the date (or approximate date) of the positive test(s). Additional surveys were completed periodically to collect information on COVID-19 vaccination. All study protocols were reviewed and approved by each site's Institutional Review Boards; study participants provided informed consent for all study activities.

Whole blood was collected in up to 40 mL samples at several time-points. Per the protocol, participants were notified to contribute a blood draw upon enrollment, after any SARS CoV-2 infection or COVID-19 vaccination dose, and approximately every three-months since their previous draw. Blood draws that were contributed by participants outside of these timepoints were accepted; for example, if a participants contributed a blood draw after four months since their last draw instead of three.

This analysis included two sub-cohorts of participants, one cohort each to separately investigate the relationship between PFAS serum concentration and post-infection antibodies and post-vaccination antibodies. Both cohorts included participants from the larger AZ-HEROES and RECOVER cohorts.

The post-infection cohort was comprised of unvaccinated participants who reported having a first-time SARS-CoV-2 infection prior to enrolling in AZ-HEROES or RECOVER, had at least one blood draw after the initial SARS-CoV-2 infection at the time of enrollment into the analysis cohort, and did not have a confirmed SARS-CoV-2 reinfection or COVID-19 vaccination prior to the first blood draw (Figure 1). There was no strict criteria for the length of time between reported infection and enrollment into the study. This cohort was selected in December 2021. Along with blood samples collected upon enrollment, additional follow-up blood samples from participants, collected approximately every three-months, were included in the analysis when available until participants received a COVID-19

vaccination dose, withdrew from the study, or had an additional confirmed SARS-CoV-2 infection. Additionally, to account for the initial expected rise in antibodies following infection, only blood draws that occurred at least 14 days after infection were included. For these participants, in-study SARS-CoV-2 infections occurred between March and December 2020, and blood samples, including follow-up samples, were collected between August 2020 and October 2021.

The post-vaccination analytic cohort was comprised of a randomly selected subset of participants who received 2 doses of either the monovalent Pfizer-BioNTech or Moderna mRNA-1273 COVID-19 vaccine or 1 dose of the Johnson & Johnson/Janssen COVID-19 vaccine, had at least one blood draw after completing the primary vaccination series, and did not have a prior self-reported or serologically confirmed SARS-CoV-2 infection at the time of vaccination (Figure 2). Along with blood samples collected shortly after the completion of the primary vaccination series, additional follow-up blood samples from participants, collected approximately every three-months, were included in the analysis for up to one year following completing the primary vaccination series or until participants received any additional or booster COVID-19 vaccination dose, withdrew from the study, or had a confirmed SARS-CoV-2 infection. Additionally, to account for the initial rise in antibodies following vaccination, only blood draws that occurred at least 14 days after completion of the primary COVID-19 vaccine series were included. For these participants, COVID-19 vaccination occurred between January and October 2021, and blood samples, including follow-up samples, were collected between January 2021 and May 2022.

Sera were sent to the University of Arizona Genetics Core laboratory for testing using a locally-developed and validated semi-quantitative enzyme-linked immunosorbent assay (ELISA) to measure antibody binding to the SARS-CoV-2 spike protein receptor binding domain (RBD) and S2 subunit domain (S2), as previously described (Ripperger et al., 2020). Anti-RBD and anti-S2 antibody levels were measured as area under the serial dilution curve (AUC) of optical density values from five serial 1:3 dilutions beginning at a 1:60 dilution of serum and ending at 1:4860. The AUC measurement is a well-established method for summarizing semi-quantitative ELISA results (Amanat et al., 2020). Compared to other units of ELISA measurement (e.g., endpoint titer), AUC values have superior coverage probabilities of serial dilution curves (Yu et al., 2012). Our final analyses included two outcomes: RBD and S2 AUC levels. Linearity of these values over time were assessed visually by plotting observed AUC values versus time since infection and vaccination, and we determined that a natural log transformation was appropriate for RBD and S2 AUC values for both cohorts. These plots can be found in the supplemental material.

Serum PFAS concentrations were quantified from a single sample from each participant. For the post-infection cohort, the first sample collected after enrolling in the study was used, and testing was conducted by the New Jersey Department of Health referencing CDC method # 6304.09. For the post-vaccination cohort, the first sample collected after vaccination was used, and testing was conducted by Eurofins (Eurofins, 2023). The change in PFAS concentrations for each participant over time during the study period was presumed minimal due to most legacy PFAS having long elimination half-lives (3 – 8.5 years). Ten PFAS analytes included in laboratory testing were quantified; however, only those with greater

than 50% of participant samples with concentration levels above the limit of detection (LOD) in both analytic cohorts were included in the final analyses. These four analytes included PFOA, PFOS, PFHxS, and PFNA. Due to different labs used for testing, total PFOA and total PFOS were able to be broken down into linear and branched PFOA and PFOS (L-PFOA, Br-PFOA, L-PFOS, Br-PFOS) for the post-vaccination cohort. More than 50% of participant samples were above the LOD for L-PFOA, L-PFOS, and Br-PFOS, but not for Br-PFOA. The full list of PFAS analytes considered for the analysis, the LOD for each analyte, and the percentage of samples greater than the LOD in each analytic cohort can be found in the supplemental material (Table S1). Any analytes within a sample that were below the LOD were imputed with the LOD divided by the square root of 2 for the final analysis (Hornung and Reed, 1990).

To estimate the association between serum PFAS concentrations and SARS-CoV-2 antibody titers, we fit linear mixed regression models (one per PFAS analyte and ELISA analyte combination) to the longitudinal data separately for each cohort. Predictors in each model included time (continuous, defined as number of weeks between initial SARS-CoV-2 infection and blood collection or number of weeks between completion of the primary COVID-19 vaccination series and blood collection), baseline PFAS analyte concentration (continuous, ng/mL), and their interaction. PFAS concentration was log-transformed to account for the right-skewness in the data. Additional self-reported fixed effect covariates included age, gender identity (male and female), race/ethnicity (non-Hispanic white, Hispanic white, non-Hispanic non-white, and Hispanic non-white), vaccine manufacturer (Pfizer and Moderna, post-vaccination cohort only), and presence of chronic conditions (categorized as none, one, and more than one comorbidity). Chronic conditions included asthma, chronic lung disease, cancer, diabetes, heart disease, hypertension, immunosuppression, kidney disease, liver disease, neurologic or neuromuscular disease or disorder, and autoimmune disease. Participants with missing vaccine manufacturer or participants who received the Johnson & Johnson vaccine were removed from the adjusted analysis to limit the comparison to mRNA vaccination. Additionally, we introduced random intercepts and slopes for the 8 study locations and occupation (categorized as health care worker, first responder, and other essential worker). These covariates were identified a priori as potential confounders (Shrotri et al., 2022). Random intercepts per individual were also included to model the likely correlation of antibody levels from the same individual over time. The key outcome was whether the difference in peak AUC values and the difference in AUC values between successive measurements depended on PFAS levels, and this was assessed using model estimates, 95% confidence intervals, and p-values. We defined peak antibody response as the AUC level at 2 weeks after infection or vaccination. To estimate the differences in peak antibody response, we used the estimated intercept from the linear mixed model; however, because the intercept represents 0 days after infection/vaccination, and we expect the peak antibody response to be delayed, we subtracted 2 weeks from the time variable (Buonfrate et al., 2021). This way, the intercept represents 2 weeks after infection/vaccination, which should be a better estimate of peak antibody response. To estimate the difference in AUC values between successive measurements, we used the time and PFAS interaction term. This term represents the difference in slopes for a unit-increase in PFAS concentration, meaning a negative value represents a steeper, or numerically lower, slope for

higher PFAS concentrations compared to lower concentrations. Statistical significance was determined using p-values estimated with a Kenward-Roger approximation with alpha equal to 0.05 (Kenward and Roger, 1997). Assumptions for the linear mixed regression models were assessed by checking fitted vs. residual plots and Q-Q plots. All statistical analyses were conducted using R version 4.2.0.

3. Results

3.1. Post-Infection

Out of 161 participants, 8 participants (5.0%) had missing covariate information and were excluded from the final analysis. The analytic set included 316 blood draws from 153 participants; 15 (9.8%) had a single blood draw, 117 (76.5%) had two blood draws, 17 (11.1%) had three blood draws, and 4 (2.6%) had four blood draws. The median number of days between infection and blood draw, including follow-up draws, was 152 days (IQR: 78–189 days). A majority of the participants were white and non-Hispanic (65.4%), female (54.2%), and had no chronic conditions (67.3%). Occupational categories included 76 (49.7%) health care personnel, 54 (35.3%) first responders, and 23 (15.0%) other essential workers. The mean age of the population was 43.2 years old, with ages ranging from 20 to 69 years old (Table 1). Distributions for the PFAS analytes were right-skewed and were positively correlated with each other; these details can be found in the supplemental material. Median, minimum, and maximum concentrations for all analytes included in the final analysis can be found in Table 1.

We fit regressions for four analytes (PFOA, PFOS, PFHxS, and PFNA) and examined the impact on RBD and S2 AUC values separately. Table 2 presents the results of the adjusted linear mixed regression models for the post-infection cohort, with estimated differences in initial peak antibody response after infection and differences in the changes to the slope of the antibody trajectories over time for each unit increase in the corresponding log-transformed PFAS and corresponding 95% confidence intervals shown. Plots with the fitted estimates for various PFAS concentrations from each of the adjusted models, as well as a table of estimates from the unadjusted models, can be found in the supplemental material.

The difference in the estimated changes to the slope of RBD (0.0006; 95% CI: [0.001, 0.01]; p = 0.014) and S2 (0.005; 95% CI: [0.00008, 0.009]; p = 0.046) antibody trajectories for each unit increase in log-transformed PFOA concentration was statistically significant, with higher concentrations associated with a slower decrease in RBD antibody levels over time.

PFOS was associated with a significant difference in initial S2 (−0.19; 95% CI: [−0.33, −0.05]; p = 0.009) antibody levels after infection, with higher PFOS concentrations being associated with a lower initial antibody response. In addition, the difference in the estimated changes to the slope of RBD (0.0008; 95% CI: [0.003, 0.01]; p = 0.003) and S2 (0.007; 95% CI: [0.002; 0.01]; p = 0.004) antibody trajectories for each unit increase in log-transformed PFOS concentration were statistically significant, with higher concentrations associated with a slower decrease in RBD and S2 antibody levels over time.

PFHxS was associated with a significant difference in initial S2 (−0.13; 95% CI: [−0.25, −0.01]; p = 0.031) antibody levels after infection, with higher PFHxS concentrations associated with a lower initial antibody response. In addition, the difference in the estimated changes to the slope of RBD (0.005; 95% CI: [0.0004, 0.009]; p = 0.034) and S2 (0.005; 95% CI: [0.0006, 0.009]; p = 0.026) antibody trajectories for each unit increase in log-transformed PFHxS concentration was statistically significant, with higher concentrations associated with a slower decrease in RBD and S2 antibody levels over time.

PFNA was associated with a significant difference in initial S2 (−0.21; 95% CI: [−0.38, −0.04]; p = 0.015) antibody levels after infection, with higher PFNA concentrations associated with a lower initial antibody response. In addition, the difference in the estimated changes to the slope of RBD (0.0006; 95% CI: [0.0004, 0.01]; p = 0.035) and S2 (0.006; 95% CI: [0.0008, 0.01]; p=0.025) antibody trajectories for each unit increase in the log-transformed PFNA concentration was statistically significant, with higher concentrations associated with a slower decrease in S2 antibody levels over time.

3.2. Post-Vaccination

A total of 880 participants were originally selected for the analysis. However, 20 (2.3%) participants were removed from the final analysis for receiving the Johnson & Johnson vaccine or missing either gender identity, race/ethnicity, vaccine manufacturer, or number of chronic conditions information. Following removal of these participants, 2451 blood draws from 860 individuals were included in the final analysis; 46 (5.3%) participants had one blood draw, 271 (31.5%) participants had two blood draws, 321 (37.3%) participants had three blood draws, 210 (24.4%) participants had four blood draws, and 12 (1.4%) participants had five blood draws. The median number of days between vaccination and blood draw, including follow-up draws, was 114 days (IQR: 25–188 days). About half (49.2%) of the participants were from Arizona. A majority of the participants were female (67.8%), non-Hispanic/white (80.6%), had no chronic conditions (61.9%), received a monovalent Pfizer COVID-19 vaccination (65.6%), and were health care workers (62.6%). The mean age of participants was 45.5 years old, with ages ranging from 21 to 79 years old (Table 3). Distributions for the PFAS analytes were right-skewed with some extreme outliers and were positively correlated with each other; these details can be found in the supplemental material. Median, minimum, and maximum concentrations for all analytes included in the final analysis can be found in Table 3.

We fit regressions for seven analytes (total and linear PFOA, total, branched, and linear PFOS, PFHxS, and PFNA) and examined the impact on RBD and S2 AUC values separately. Table 4 presents the results of the adjusted linear mixed regression models for the post-vaccination cohort, with estimated differences in initial peak antibody response after vaccination and differences in the changes to the slope of the antibody trajectories over time for each unit increase in the corresponding log-transformed PFAS and corresponding 95% confidence intervals shown. Plots with the fitted estimates for various PFAS concentrations from each of the adjusted models, as well as a table of estimates from the unadjusted models, can be found in the supplemental material.

In all 14 models, there were no statistically significant relationships between serum PFAS concentration and differences in peak antibody response after vaccination, as well as serum PFAS concentration and differences in the changes in antibody levels over time after vaccination. Along with not being not statistically significant, all estimates were near the null. Notably, a one-unit increase in log-transformed total PFOA concentration was estimated to be associated with a 0.02 higher log-transformed RBD AUC value 2 weeks after vaccination (95% CI: [−0.02, 0.06]) and a 0.0003 lower slope of log-transformed RBD AUC values over time (95% CI: [−0.002, 0.001]), and a one-unit increase in log-transformed total PFOS concentration was estimated to be associated with a 0.01 higher log-transformed RBD AUC value 2 weeks after vaccination (95% CI: [−0.02, 0.05]) and a 0.0003 higher slope of log-transformed RBD AUC values over time (95% CI: [−0.0008, 0.001]).

4. Discussion

In this study we found an association between serum PFAS concentration and SARS-CoV-2 antibody levels following infection, but not after vaccination. In our post-infection cohort, a higher PFAS concentration, as measured by several analytes, was estimated to result in a lower initial antibody response and a slower decline of antibodies over time after SARS-CoV-2 infection. These results suggest that higher serum concentrations of PFAS can result in lower antibody levels following initial infection and potentially reduced protection against future SARS-CoV-2 infection.

For the post-infection cohort, the lower initial immune response suggests the possibility of decreased protection against recurrent SARS-CoV-2 infection among individuals with higher PFAS concentrations. Multiple studies have demonstrated that higher antibody levels are associated with a lower risk of COVID-19 disease (Fu et al., 2022; Gilbert et al., 2022; Gilboa et al., 2022; Lee et al., 2023). Additionally, antibodies being measured via SARS-CoV-2 ELISA directly correlate with neutralization of live SARS-CoV-2 virus (Ripperger et al., 2020; Stone et al., 2022). Specifically receptor binding domain (RBD) reactive antibody titers quantified via AUC from the identical SARS-CoV-2 ELISA tests used in this analysis correlated strongly with neutralization of the USA-WA1/2020 strain of SARS-CoV-2 in plaque reduction neutralization testing (PRNT) in direct serological studies (Ripperger et al., 2020). Results from these functional neutralization studies also suggest that higher levels of binding antibodies may be associated with reduced risk of COVID-19. While the slower decline in antibody levels associated with high PFAS concentrations for the post-infection cohort was unanticipated, it is consistent with having lower initial antibody responses and therefore less of a potential decline as humoral antibody levels over time. For the post-infection cohort, there were slight differences in the magnitude of the relationship between serum PFAS and RBD antibodies versus S2 antibodies. This may partially be due to differing responses of RBD and S2 antibodies after SARS-CoV-2 infection (Ladner et al., 2021; Meyers et al., 2022).

While these results suggest that elevated PFAS levels impede potential immune response to infection by blunting peak antibody levels following SARS-CoV-2 infection, this may not be the case for immune response to COVID-19 vaccination. Studies evaluating the relationship

between antibody response and vaccination for other vaccines have generally found an inverse relationship although findings are heterogenous.

A small study of 12 adults in Denmark reported negative associations between diphtheria antibody levels and serum concentrations of PFOS, PFDA, PFNA, PFUnDA, and perfuorododecanoic acid (PFDoDA) (Kielsen, 2016). Looker (2014) found that U.S. adults (N = 403) with elevated PFOA serum concentrations had reduced antibody titer rise to A/H3N2 influenza vaccine. However, a study of the general U.S. population that looked at associations between PFOA or PFOS and rubella antibody titers found a negative association between PFOA and adult men, but not women (Pilkerton et al., 2018) and in a study with adults in China, PFOS, but not PFOA, was inversely associated with hepatitis B surface antibodies (Zeng et al., 2020).

The concentrations of serum PFAS observed in this study were slightly lower compared to the United States population as published in the 2017–2018 National Health and Nutrition Examination Survey (NHANES), particularly for PFOA and PFOS (CDC, 2022). The general US population had a median PFOA and PFOS concentration of 1.47 and 4.3 ng/mL, compared to 0.9 and 2.2 for the post-infection cohort, and 1.1 and 3.3 for the post-vaccination cohort, respectively. Although lower serum PFAS concentrations were observed in our study, it has been shown that serum PFAS concentrations are decreasing over time within the general population; it is likely that a more recent survey of the general population might be more representative for comparison given the time displacement between blood collections from our cohorts and the latest NHANES data (ATSDR, 2022).

This study is subject to multiple limitations. First, there is a potential for bias introduced by the selection of participants. Our selected sample only includes participants who contributed at least one whole blood sample after infection or vaccination; however, there are a number of participants in the AZ-HEROES and RECOVER cohorts who had a SARS-CoV-2 infection prior to study enrollment or received a primary COVID-19 vaccination but did not contribute any whole blood samples. If there is a relationship between missingness of whole blood samples and post-recovery SARS-CoV-2 or post-vaccination serologic antibody levels and PFAS, our results may be biased. Second, for the post-infection cohort, SARS-CoV-2 infection was self-reported by participants prior to enrolling in the study, and little information about the severity or length of the infection was available because the infections occurred prior to joining the AZ-HEROES or RECOVER cohorts. Additionally, misclassification of prior infection may have occurred for some participants. Third, cellular immunity was not analyzed for these blood samples, which could be important for understanding protection against severe disease. Fourth, because of the number of models fit, there is potential for multiplicity bias. Finally, this study did not explore the mechanisms for the relationship between serum PFAS and immune response to SARS-CoV-2 infection or COVID-19 vaccination.

This study had several strengths. First, the repeated measures of SARS-CoV-2 antibodies over an extended period allowed for the investigation of both peak and decline of antibodies over time following SARS-CoV-2 infection and COVID-19 vaccination. By utilizing a mixed model, we were able to estimate peak antibody response after SARS-CoV-2 infection

and COVID-19 vaccination, even if not all participants contributed a blood draw during this time window. Second, this study utilized two different measurements of antibody levels and four and seven different PFAS analytes for the post-infection and post-vaccination cohorts respectively, which helps broaden the scope of the findings. Finally, participants completed weekly testing for SARS-CoV-2 via PCR and frequent vaccination surveys once enrolled in AZ-HEROES/RECOVER, which made it unlikely for any blood draws included in the analysis to violate our exclusion criteria, such as blood draws occurring after a repeat SARS-CoV-2 infection or after an additional COVID-19 vaccine dose.

5. Conclusion

From this research, we found a potential relationship between serum PFAS concentration and antibody response following a SARS-CoV-2 infection but found no evidence of a relationship following completion of a primary COVID-19 vaccination series. Future directions for research regarding PFAS and SARS-CoV-2 include exploring the mechanisms between the relationships shown in this analysis and investigating the relationship between PFAS concentration and its effect on protection against SARS-CoV-2 infection.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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- Effect of serum PFAS on immune response to COVID-19 examined here.
- Found relationship between serum PFAS and post-SARS-CoV-2 infection immune response.
- High serum PFAS concentration may dampen response to SARS-CoV-2 infection.

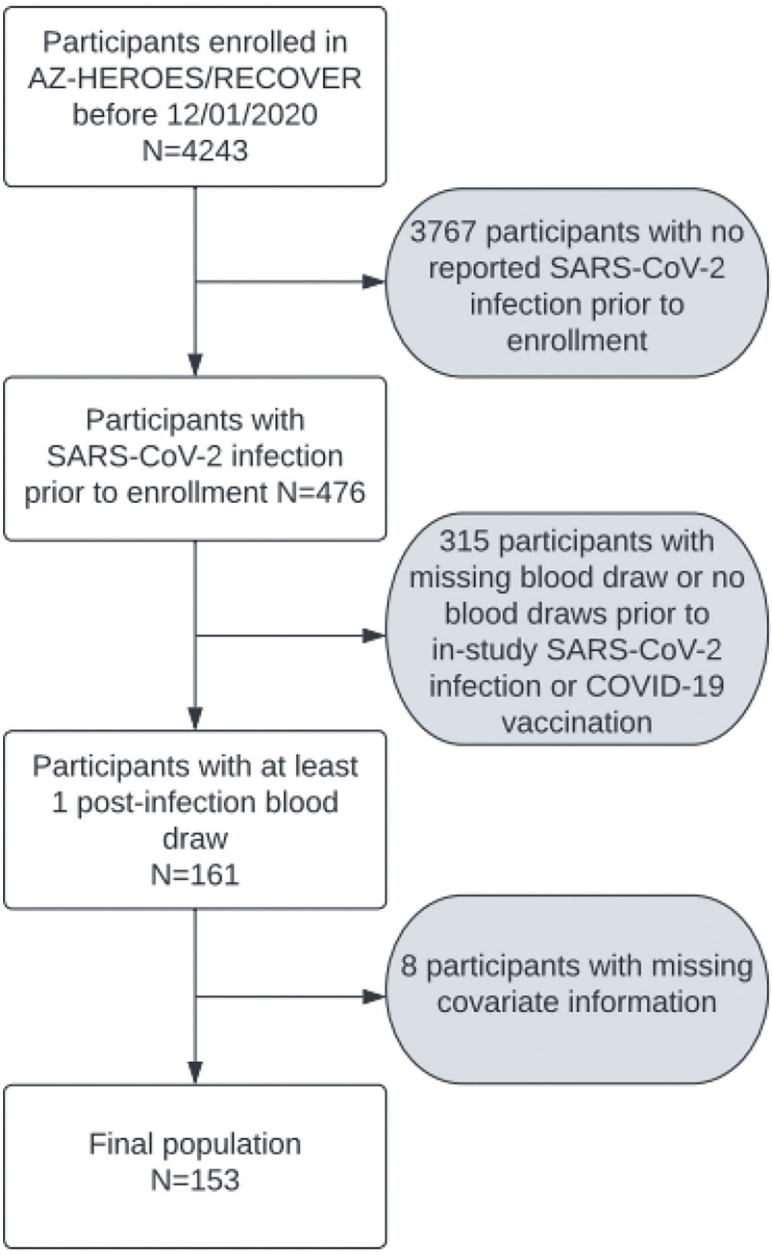

Figure 1.
Flowchart for determination of final population for post-infection analysis from the AZ-HEROES/RECOVER cohorts.

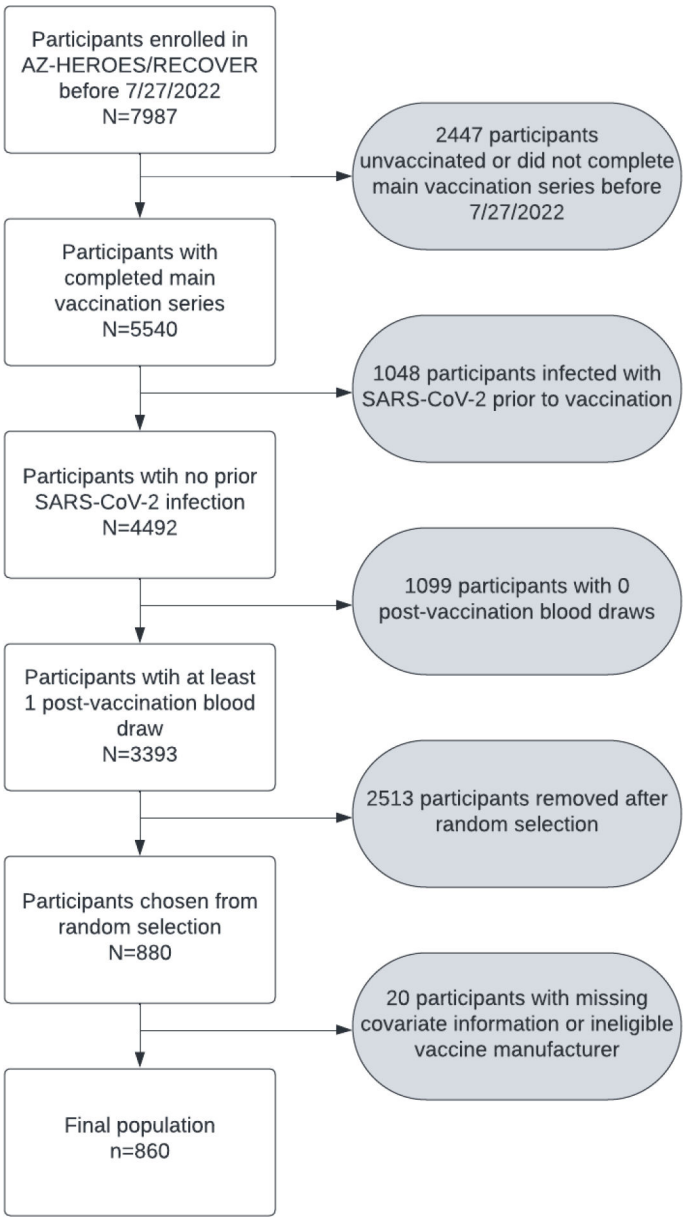

Figure 2.

Flowchart for determination of final population for post-vaccination analysis from the AZ-HEROES/RECOVER cohorts.

Table 1.

Demographic information of post-infection analytic set from AZ-HEROES/RECOVER cohort (n=153).

Variable	n (%) or Mean (SD)
Occupation[a]	
Health Care Worker	76 (49.7)
First Responder	54 (35.3)
Other Essential Worker	23 (15.0)
Site	
Tucson, AZ	35 (22.9)
Phoenix, AZ	23 (15.0)
Other areas in AZ	12 (7.8)
Miami, FL	38 (24.8)
Temple, TX	8 (5.2)
Portland, OR	6 (3.9)
Duluth, MN	15 (9.8)
Salt Lake City, UT	16 (10.5)
Age, yrs	43.2 (11.5)
Number of Chronic Conditions[b]	
None	103 (67.3)
One	36 (23.5)
Two or More	14 (9.2)
Gender Identity	
Female	83 (54.2)
Male	70 (45.8)
Race/Ethnicity	
White/Non-Hispanic	100 (65.4)
White/Hispanic	44 (28.8)
Non-White/Non-Hispanic	9 (5.9)
Number of Blood Draws	
One	15 (9.8)
Two	117 (76.5)
Three	17 (11.1)
Four	4 (2.6)
PFAS Analyte	Median (Min, Max), ng/mL
PFOA	0.9 (0.1, 5.8)
PFOS	2.2 (0.3, 17.9)
PFNA	0.33 (0.06, 2.34)
PFHxS	1.03 (0.05, 9.89)

[a]Other essential workers include occupation sectors with potentially high exposures to SARS-CoV-2 such as education, agriculture, public transportation services, waste collection, delivery, utilities, community-based services, childcare, and others (Lutrick, 2021; Edwards, 2021).

[b]Chronic conditions included asthma, chronic lung disease, cancer, diabetes, heart disease, hypertension, immunosuppression, kidney disease, liver disease, neurologic or neuromuscular disease or disorder, and autoimmune disease.

Abbreviations: PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonic acid; PFUnDA, perfluoroundecanoate; PFBS, perfluorobutane sulfonate; PFDA, perfluorodecanoate; PFHxS, perfluorohexane sulfonic acid; PFNA, perfluorononanoic acid.

Table 2.

Parameter estimates from regression models assessing the relationship between baseline PFAS levels and peak antibody response (Peak) and antibody decline over time (Slope) for RBD and S2 immune markers for post-infection cohort

	RBD AUC		S2 AUC	
PFAS Analyte	**Peak (95% CI)[a]**	**Slope (95% CI)[b]**	**Peak (95% CI)[a]**	**Slope (95% CI)[b]**
PFOA	−0.15 (−0.33, 0.02)	**0.0006 (0.001, 0.01)**	−0.10 (−0.25, 0.04)	**0.005 (0.00008, 0.009)**
PFOS	−0.16 (−0.33, 0.01)	**0.0008 (0.003, 0.01)**	**−0.19 (−0.33, −0.05)**	**0.007 (0.002, 0.01)**
PFHxS	−0.12 (−0.26, 0.02)	**0.005 (0.0004, 0.009)**	**−0.13 (−0.25, −0.01)**	**0.005 (0.0006, 0.009)**
PFNA	−0.17 (−0.37, 0.03)	**0.0006 (0.0004, 0.01)**	**−0.21 (−0.38, −0.04)**	**0.006 (0.0008, 0.01)**

One model per each ELISA outcome/PFAS analyte combination, with an estimated peak and slope difference in each model.

[a]Mean difference in antibody levels at week 0 after adjusting for age, gender, number of chronic conditions, and race/ethnicity as fixed effects and with random intercepts and slopes for site and occupation.

[b]Change in the antibody trajectory over time for each unit increase in associated PFAS after adjusting for age, gender, number of chronic conditions, and race/ethnicity as fixed effects and with random intercepts and slopes for site and occupation. Estimated from the interaction coefficient of time and PFAS analyte.

Bold signifies statistically significant at alpha = 0.05. P-values estimated with a Kenward-Roger approximation.

Abbreviations: CI, confidence interval; RBD, receptor-binding domain; AUC, area under the curve; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonic acid; PFHxS, perfluorohexane sulfonic acid; PFNA, perfluorononanoic acid.

Table 3.

Demographic information of post-vaccination analytic set from AZ-HEROES/RECOVER cohort (n=860).

Variable	n (%) or Mean (SD)
Occupation[a]	
Health Care Worker	538 (62.6)
First Responder	129 (15.0)
Other Essential Worker	193 (22.4)
Site	
Tucson, AZ	266 (30.9)
Phoenix, AZ	83 (9.7)
Other areas in AZ	74 (8.6)
Miami, FL	19 (2.2)
Temple, TX	30 (3.5)
Portland, OR	200 (23.3)
Duluth, MN	156 (18.1)
Salt Lake City, UT	32 (3.7)
Age, yrs	45.5 (10.8)
Number of Chronic Conditions	
None	532 (61.9)
One	163 (19.0)
Two or More	165 (19.2)
Gender Identity	
Female	583 (67.8)
Male	277 (32.2)
Race/Ethnicity	
White/Non-Hispanic	693 (80.6)
White/Hispanic	82 (9.5)
Non-White/Non-Hispanic	70 (8.1)
Non-White/Hispanic	15 (1.7)
Vaccine Manufacturer	
Pfizer	564 (65.6)
Moderna	296 (34.4)
Number of Blood Draws	
One	46 (5.3)
Two	271 (31.5)
Three	321 (37.3)
Four	210 (24.4)
Five	12 (1.4)
PFAS Analyte	Median (Min, Max), ng/mL
Total PFOS	3.3 (0.1, 130.0)
Br-PFOS	0.7 (0.1, 40.0)

Variable	n (%) or Mean (SD)
L-PFOS	2.5 (0.1, 87.0)
Total PFOA	1.1 (0.2, 7.2)
L-PFOA	1.1 (0.2, 7.2)
PFHxS	0.9 (0.1, 23.0)
PFNA	0.4 (0.1, 6.8)

[a]Other essential workers include occupation sectors with potentially high exposures to SARS-CoV-2 such as education, agriculture, public transportation services, waste collection, delivery, utilities, community-based services, childcare, and others (Lutrick, 2021; Edwards, 2021).

[b]Chronic conditions included asthma, chronic lung disease, cancer, diabetes, heart disease, hypertension, immunosuppression, kidney disease, liver disease, neurologic or neuromuscular disease or disorder, and autoimmune disease.

Abbreviations: PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonic acid; PFHxS, perfluorohexane sulfonic acid; PFNA, perfluorononanoic acid.

Table 4.

Parameter estimates from regression models assessing the relationship between baseline PFAS levels and peak antibody response (Peak) and antibody decline over time (Slope) for RBD and S2 immune markers for post-vaccination cohort

	RBD AUC		S2 AUC	
PFAS Analyte	**Peak (95% CI)[a]**	**Slope (95% CI)[b]**	**Peak (95% CI)[a]**	**Slope (95% CI)[b]**
Total PFOA	0.02 (−0.02, 0.06)	−0.0003 (−0.002, 0.001)	−0.005 (−0.04, 0.04)	0.0009 (−0.0005, 0.002)
Total PFOS	0.01 (−0.02, 0.05)	0.0003 (−0.0008, 0.001)	0.01 (−0.02, 0.05)	0.0004 (−0.0007, 0.001)
Br-PFOS	0.02 (−0.01, 0.06)	0.00001 (−0.001, 0.001)	0.01 (−0.02, 0.05)	0.0002 (−0.0009, 0.001)
L-PFOS	0.01 (−0.02, 0.05)	0.0004 (−0.0007, 0.001)	0.01 (−0.02, 0.05)	0.0004 (−0.0007, 0.002)
L-PFOA	0.02 (−0.02, 0.06)	−0.0003 (−0.002, 0.001)	−0.005 (−0.05, 0.04)	0.0009 (−0.0005, 0.002)
PFHxS	0.005 (−0.02, 0.03)	0.0006 (−0.0004, 0.002)	−0.004 (−0.03, 0.03)	0.0001 (−0.0008, 0.001)
PFNA	0.02 (−0.02, 0.06)	−0.0008 (−0.002, 0.0006)	0.006 (−0.04, 0.05)	0.0003 (−0.001, 0.002)

One model per each ELISA outcome/PFAS analyte combination, with an estimated peak and slope difference in each model.

[a]Mean difference in antibody levels at week 0 after adjusting for age, gender, number of chronic conditions, vaccine manufacturer, and race/ethnicity as fixed effects and with random intercepts and slopes for site and occupation.

[b]Change in the antibody trajectory over time for each unit increase in associated PFAS after adjusting for age, gender, number of chronic conditions, vaccine manufacturer, and race/ethnicity and with random intercepts and slopes for site and occupation. Estimated from the interaction coefficient of time and PFAS analyte.

Bold signifies statistically significant at alpha = 0.05. P-values estimated with a Kenward-Roger approximation.

Abbreviations: CI, confidence interval; RBD, receptor-binding domain; AUC, area under the curve; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonic acid; PFHxS, perfluorohexane sulfonic acid; PFNA, perfluorononanoic acid.