**메ㅔProtective effectiveness of SARS-CoV-2 infection risk between hybrid and vaccine-induced immunity against the omicron variant, K-SEROSMART**

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**Abstract (290 words)**

**Background:** Vaccine effectiveness may wane over time, but how this affects real-world infection risk remains unclear. Assessing risk after an Omicron wave is also challenging due to unconfirmed infections. We examined infection risks in hybrid and vaccine-induced immunity populations, accounting for both confirmed and unconfirmed infections from nationwide surveillance in South Korea.

**Methods:** We identified hybrid and vaccine-only groups using S and N serology. Infection outcomes were defined by confirmed dates and N seroconversion between August and December 2022. Two outcomes were analyzed: confirmed infections from the KDCA database, and unconfirmed infections based on N seroconversion (vaccine group) or antibody titer increases (hybrid group). We compared survival curves for both groups under conservative (confirmed only) and inclusive (confirmed + unconfirmed) definitions.

**Results:** Comparing conservative and inclusive outcome definitions, the hybrid immunity group exhibited a substantial difference, with survival decreasing from 98% to 80%, while the vaccine immunity group showed survival rates of 70% and 60%, respectively, shifting the hazard ratio between the two groups from fivefold to twofold over four months. In hybrid and vaccine immunity groups, females face higher hazard rates than males (31% and 26% higher under the inclusive outcome versus 88% and 25% higher under the conservative outcome). Across both outcome definitions, the youngest age group in the vaccine-induced cohort exhibited lower survival probabilities than middle age groups, with individuals aged <20 showing a statistically 61% higher hazard rate than those aged 40–59 under the conservative definition. (다른그룹연령까지 차례대로 언급)

**Conclusion:** Females and individuals under 20 without prior infections and booster vaccinations face higher risks than middle aged adults. These findings underscore the importance for public health authorities to prioritize COVID-19 vaccination among females and children through targeted campaigns and tailored communication strategies.

General population + inclusive outcome through seroprev data

Difference: hybrid vs vaccine: Conservative 28% vs inclusive 20%

Under conservative data only, many studies mainly compared hybrid vs vaccine / naïve 🡪 to say infected people also better to be vaccinated

Hybrid: 2% to 20%

Vaccine: 30% to 40%

하이브리드에 unconfirmed infection이 많이 들어간다는 측면보다,

**Introduction**

Both natural SARS-CoV-2 infection and COVID-19 vaccination play crucial roles in developing population-level immunity [1]. While immune responses are complex and multifaceted, epidemiological studies often rely on measurable indicators like antibodies to assess population immunity and the durability of antibody responses following infection and/or vaccination [2]. Several epidemiological studies show that hybrid immunity had the highest magnitude and durability of protection against all outcomes, emphasizing the importance of providing vaccination to previously infected individuals as infection-induced protection against reinfection wanes rapidly, but vaccination further increases durability [3–5]. However, the extent and duration of hybrid immunity’s waning—especially following Omicron infections—remain largely uncharacterized. Complicating efforts to measure and compare this protection is the widespread rise of the Omicron (B.1.1.529) variant, which has led to a significant number of individuals possessing hybrid immunity (a result of both infection and vaccination). Disparate rates and timings of past infections, variations in vaccine types and number of doses, and evolving variants of concern capable of evading existing immunity present additional challenges in estimating the overall magnitude and durability of this protection [6].

A recent systematic review of SARS-CoV-2 vaccine effectiveness studies estimated the durability of protection conferred by previous infection combined with previous vaccination (i.e., hybrid immunity) and previous infection alone against multiple clinical outcomes of SARS-CoV-2 infection caused by the omicron variant [3] [7]. This review found that although both infection-induced and hybrid immunity against Omicron infection waned rapidly, they provided high and sustained protection against hospital admission or severe disease compared to vaccination alone. However, much of the existing research on SARS-CoV-2 seroprevalence-based immunity has focused on specific groups—such as healthcare workers or immunocompromised individuals [8]), leaving the magnitude and durability of immune protection in the general population less thoroughly explored [9,10]. Moreover, most large-scale seroprevalence studies across various countries primarily account for laboratory-confirmed infections, overlooking a potentially sizable number of unreported or asymptomatic cases [11–13].

In August 2022, the nationwide Korea Seroprevalence Study of Monitoring of SARS-CoV-2 Antibody Retention and Transmission (K-SEROSMART) was launched to examine the extent of COVID-19 infections—including unrecognized cases—across local communities through longitudinal cohort surveillance [5]. The study revealed that most individuals had SARS-CoV-2 antibodies and uncovered a substantial number of previously undetected cases. With new Omicron sub lineages continually challenging existing vaccines, there remains a knowledge gap regarding how vaccination and infection influence long-term protection across diverse subgroups respectively. Addressing these gaps is crucial for refining booster recommendations, prioritizing high-risk populations, and anticipating future changes in SARS-CoV-2 epidemiology. This research pursued two primary objectives: first, to compare survival probabilities and hazard ratios of breakthrough infections between hybrid and vaccine-only immunity groups, taking into account both confirmed and unconfirmed infection events; second, to evaluate how these infection hazard rates vary by age, sex, and number of vaccine doses within each immunity category. By shedding light on which populations are most susceptible to breakthrough infections and the relative durability of both hybrid and vaccine-induced protection, these findings provide valuable evidence for tailoring targeted interventions and optimizing long-term immunization strategies in diverse community settings.

**Methods**

**Participants.** The fieldwork for K-SEROSMART Wave 1 was conducted between August 12 and September 5, 2022, with a total of 9,945 individuals from 5,041 households participating, across 258 communities, representing all basic local governments in South Korea. During face-to-face household interviews, participants self-reported health status, demographic and socioeconomic characteristics. Subsequently, participants visited a community health center or medical clinic for blood sampling. The details of the baseline study were provided in our initial investigation. In December 2022, the subsequent second survey (Wave 2) was conducted involving serial sampling of the same population from K-SEROSMART Wave 1 to estimate the change in immunity, reinfection rates, and effectiveness of COVID-19 vaccinations, 4 months after the initial survey. A total of 8,826 individuals were contacted, of whom 7,528 completed K-SEROSMART Wave 2. More detailed descriptions of the cohort study design and data collection methods are published elsewhere [14]. All public health centers and medical institutions in Korea are required to report the results of expert rapid antigen tests and emergency reverse transcription polymerase chain reaction (RT-PCR) screening tests for newly confirmed COVID-19 cases to the COVID-19 information management system of the KDCA within 24 hours. For participants in the survey, the names, sex, dates of birth, and home addresses of those who consented to the use of their personal information were used to link the survey data with their COVID-19 confirmation and vaccination history information provided by the KDCA [14].

**Sample Collection and Definitions.** The serum samples were analyzed for SARS-CoV-2 antibodies using the Elecsys Anti-SARS-CoV-2 test (Roche). Blood samples were analyzed for the presence of antibodies to spike proteins (anti-S) and antibodies to nucleocapsid proteins (anti-N) SARS-CoV-2 proteins using an electrochemiluminescence immunoassay. The results of the anti-S assay were presented numerically and deemed positive for anti-S when the cut-off index was greater than or equal to 0.80 U/mL, signifying the formation of antibodies due to natural infection or vaccination [15]. The results of the anti-N assay were classified as reactive or non-reactive, with a specified cut-off index. A cut-off index of 1.0 or higher indicated an anti-N result of reactive, meaning that the patient tested positive for anti-N; this suggested that antibodies had previously formed due to natural infection [15].

A diagram of a vaccine

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Figure 1: Flow Chart Illustrating the Cohort Study Design

**Inclusion/Exclusion criteria.** In this analysis, we defined the cohort by the following four distinct immunity types: hybrid-induced immunity (*S*+*N* +) [16,17], vaccine-induced immunity (*S*+*N−*), infection-induced immunity (*S−N* +), and naive (*S−N−*). Notably, following the Omicron wave in South Korea, the majority of the population (88%) exhibited either hybrid or vaccine-induced immunity, with only 8% showing infection-induced immunity and 2% remaining without immunity as of August 2022. Consequently, subsequent research focused primarily on the hybrid and vaccine-induced immunity groups. The demographic and clinical characteristics of these two groups are detailed in Table 1.

**Newly confirmed cases of COVID-19:**We analyzed two primary outcomes: First, the occurrence of any (confirmed or unconfirmed) infection events between the 1st and 2nd surveillance based on N antibody seroconversion (from N nonreactive to active) for vaccine-induced immunity and N antibody titer level increase for the hybrid induced immunity group. Second, the occurrence of confirmed infection events based on the KDCA database between the K-SEROSMART Wave 1 and Wave 2 surveillance and (Figure 1) To ensure the validity of our assessment of the difference of infection risks by the immunity status measured at the Wave 1, we implemented the following exclusion criteria: First, since we do know the exact timing of unconfirmed infection, we excluded those who had any vaccination between the Wave 1 and Wave 2. Second, since we know the exact timing of vaccination and confirmed infection from the KDCA database, we excluded those who had vaccination prior to the infection event. Accordingly, the infection events defined by N antibody status/level are considered as inclusive outcomes and the infection events defined by confirmation are considered as conservative outcomes.

**Statistical analyses**. We assessed survival analyses based on the two different outcome definitions: 1) conservative outcomes (confirmed infections); and 2) inclusive outcomes (confirmed and unconfirmed infections) to compare the vaccine-induced and hybrid-induced immunity groups and to compare the subgroups within each immunity group. We imputed missing infection dates for unconfirmed cases using the {mice} R package and the predictive mean matching (PMM) method [18]. Missing infection date was converted into the time gap after the first surveillance, and a regression model was fitted using predictors such as age, sex, vaccine doses, underlying diseases, time since the latest immunological assessment, S antibody levels and N antibody levels at the Wave 1. The regression model estimated time gaps for observed cases (confirmed infections), and for each missing value among unconfirmed infections, the method identified the k-nearest gaps from observed data (individual characteristics of confirmed infection cases) based on absolute differences between predicted and observed time gaps. From these k-nearest gaps, one was randomly selected to impute the missing infection time. This approach ensured that the imputed dates aligned with the distribution of confirmed infections, preserving the inherent variability. Unlike mean or median imputation, PMM maintains the original data structure and variability, preventing over-smoothing that could distort survival patterns [19]. Furthermore, PMM performs particularly well with datasets containing a mix of continuous and categorical predictors, making it especially suitable for the covariates in this study. By systematically addressing missing data, our study enabled a comparison between survival analysis results based on conservative (confirmed infection only) and inclusive (confirmed and unconfirmed infection) outcomes for the vaccine-induced and hybrid-induced immunity groups.

The survival probabilities between vaccine-induced and hybrid-induced groups were compared using Kaplan-Meier survival curves, stratified by age to account for potential age-related differences. Age-based weights were incorporated into the survival model. We examined the hazard ~~rate~~ ratios (i) between hybrid and vaccine immunity groups and (ii) among the subgroups within each immunity group. First of all, we tested the Cox proportional hazards assumption—requiring hazard ratios to remain constant over time—using the R package {survival} [20,21] and evaluated the effects of each of the covariates, such as sex, age, vaccine doses, the time since the latest immunology assessment, and other factors on hazard ratio while adjusting for potential confounding variables. We also calculated Schoenfeld residuals and evaluated the effects of each of the covariates, such as sex, age, vaccine doses, the time since the latest immunology assessment, and other factors on hazard ratio while adjusting for potential confounding variables. We also calculated Schoenfeld residuals and performed regression against time to identify any systematic trends or deviations, and chi-squared tests for each covariate and the overall model to confirm adherence to the assumption. We were unable to fit the Cox model to estimate hazard ratios between the hybrid-induced and vaccine-induced groups as it failed to meet the proportional hazard assumptions due to fluctuations in the hazard rate ratio between the two groups over the four-month follow-up period. (Appendix Table S1 and S2) Alternatively, we calculated direct hazard rates separately for each month and performed log-rank tests for each monthly interval, as detailed in Table 3. After several hazard assumptions tests (Likelihood ratio test, Wald test, log-rank test), we could fit the weighted Cox proportional hazards models to compare the hazard ratio among the age subgroups within each immunity group (Table 4). In this process, the other covariates (underlying diseases, time since the latest immunological assessment, S antibody levels and N antibody levels at the Wave 1) were excluded from the final model as they violated the proportional hazards assumption (p < 0.05), indicating that their effects on the hazard ratio change over time.

**Results****.**

As shown in Table 1, the hybrid‐induced (S+N+) and vaccine‐induced (S+N–) groups differed significantly in several demographic and clinical characteristics. Compared to the vaccine‐induced cohort, the hybrid‐induced group was significantly younger (p<0.001), had fewer comorbidities (p<0.001), and reported more recent immunologic events (74% had their latest immunological event within 6 months versus 37% in the vaccine‐only group). They were also less likely to have received four vaccine doses before Wave 1 (13% versus 25%; p<0.001). By contrast, there were no significant differences in sex or BMI. In terms of outcomes, COVID‐19 infection frequencies between and after Waves 1 and 2 differed significantly (p<0.001) between the two groups. The hybrid-induced immunity group exhibited substantially lower infection rates than the vaccine-induced group across both outcome definitions, with conservative infection outcomes (2% versus 21%) and inclusive infection outcomes (12% versus 26%), respectively. This pattern is further reflected in the confirmation status distribution: within the hybrid-induced group, merely 11% of infections were test confirmed while 89% remained unconfirmed (ratio ~8:1). Conversely, the vaccine-induced immunity group demonstrated an inverse relationship, with 77% of infections receiving laboratory confirmation versus 23% remaining unconfirmed (ratio ~3:1).

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Table 1: Summary table of cohort study design

|  |  |
| --- | --- |
| Figure 2: Kaplan-Meier Survival Curves and Survival Tables for Hybrid- and Vaccine-induced Groups | |
| 1. Conservative outcome definitions | 1. Inclusive outcome definitions |
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| 1. Conservative outcome definitions by age groups | 1. Inclusive outcome definitions by age groups |
| A graph of a graph  AI-generated content may be incorrect.  A table with numbers and a few months  AI-generated content may be incorrect. | A graph of different colored lines  AI-generated content may be incorrect.  A table with numbers and a few months  AI-generated content may be incorrect. |

Note: In the survival table, the values within each parenthesis indicate the number of confirmed cases for Panel A and the number of confirmed and unconfirmed cases for Panel B.

Figure 2 presents Kaplan-Meier survival curves depicting the likelihood of remaining COVID-19 infection-free over time, based on conservative (Panel A) and inclusive (Panel B) outcome definitions. The analysis compares vaccine-induced and hybrid-induced immunity cohorts over a 4-month period between Wave 1 and Wave 2 surveillances. Comparing outcomes based on the conservative versus inclusive definitions, the vaccine-induced group showed similar survival probabilities—approximately 70% with the conservative definition versus 60% with the inclusive definition—by the end of the observation period. In contrast, the hybrid immunity group displayed a marked difference: survival remained at 98% under the conservative definition but dropped to 80% under the inclusive definition. For both outcome definitions, the <20 age group in the vaccine-induced cohort exhibited a lower and rapid decrease in survival probabilities compared to older age groups. Under the inclusive outcome definition, the youngest age group in the hybrid immunity cohort, however, consistently showed a higher survival probability compared to older age groups. Under the conservative definition, no significant age-based differences were observed in the hybrid immunity cohort—likely due to the small number of events.

|  |  |
| --- | --- |
| Table 2: Comparison of Monthly Hazard Rates Between Hybrid-Induced and Vaccine-Induced Groups | |
| 1. Infection based on conservative outcome definitions | 1. Infection based on inclusive outcome definitions |
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Under the inclusive outcome definition, the hybrid-induced group demonstrated monthly hazard ratios that were about 5 times higher than those of the vaccine-induced group in the first month, gradually decreasing to around 2 times higher by the fourth month. In comparison, the monthly hazard ratios between the vaccine and hybrid groups were substantially higher (>6 times) under the conservative outcome definition than under the inclusive outcome definition due to a very small number of confirmed infections in the hybrid group, especially early in the follow-up. The subsequent decrease in these ratios over time may suggest faster immunity waning in the vaccine-only group or a gradual convergence of immunity levels. Log-rank tests were performed for each month, and all results indicated statistically significant differences between the groups.

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| --- | --- |
| Table 3. Weighted Cox Proportional Hazards Model Results | |
| 1. Infection based on conservative outcome definitions | 1. Infection based on inclusive outcome definitions |
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In both hybrid and vaccine immunity groups, females exhibit significantly higher infection hazard rates than males, with a 31% and 26% increase under the inclusive outcome definition and an 88% and 25% increase under the conservative outcome definition, respectively. In the vaccine immunity group, individuals aged <20 exhibited a statistically 61% higher hazard rate compared to those aged 40-59 under the conservative outcome definition. The inclusive outcome captures more unconfirmed infections among older populations than the conservative outcome (as shown in Appendix Table S3), leading to a 40% lower hazard ratio in the youngest age group compared to those aged 40–59 in the hybrid immunity group. In both hybrid and vaccine immunity groups, the additional vaccine dose was not significantly associated with reducing the hazard ratio. Finally, the lack of a protective effect from additional vaccine doses in either group raises the possibility of a “ceiling effect” - where each additional vaccine dose adds less marginal benefit - among the hybrid-immune or timing and coverage issues in the vaccine-only population. This underscores the need for more nuanced booster strategies and continued surveillance to optimize protection.

# **Discussion**

Our study examined the protective effectiveness of COVID-19 immunity between hybrid immunity and vaccine-induced immunity in the general population using community-based nationwide surveillance in South Korea after an Omicron variant epidemic wave [22]. Comparing conservative and inclusive outcome definitions, the hybrid immunity group exhibited a substantial difference, with survival decreasing from 98% to 80%, while the vaccine immunity group showed survival rates from 70% to 60%, respectively. Under the inclusive outcome, more unconfirmed infections among older populations with recent exposures were included in infection risks than the conservative outcome. This resulted in the individuals aged <20 having a lower risk than those aged 40-59 in both immunity groups, especially with a significantly lower hazard rate (40%) among the hybrid immunity group. Under the conservative definition, the individuals aged <20 in the vaccine-induced cohort exhibited lower survival probabilities than older age groups, showing a significantly higher hazard rate (61%) than those aged 40–59. This is likely because the majority of the youngest in the vaccine group did not receive a booster or had a longer time since their last vaccination, leading to lower immunity and survival probabilities. In both hybrid and vaccine immunity groups, females had higher hazard rates (31% and 26% higher under the inclusive outcome and 88% and 25% higher under the conservative outcome, respectively) than males, suggesting possible sex-based differences in exposure, immune response, or healthcare-seeking behavior [23].

Our results reveal a substantial discrepancy in risk patterns between conservative and inclusive outcome definitions across both immunity groups. By comparing confirmed and unconfirmed infections—evidenced by increases in case counts without corresponding test confirmation (Table S1), particularly among individuals with recent (<1 month) immunological events (4% vs. 35% in the hybrid group; 5% vs. 37% in the vaccine-only group). This likely reflects asymptomatic or mild cases for which individuals did not seek diagnostic testing. The gap is especially pronounced among the older population in the hybrid immunity group, contributing to marked differences in survival probabilities depending on the outcome definition used.

In terms of age-based risk differences, over 90% of South Korean adults (aged >20) received primary vaccinations, yet coverage among younger populations was substantially lower—only 1.1% of children aged 5–11 and 66% of those aged 12–17 was vaccinated as of January 2023 [24,25]. Winter booster uptake in 2022 was also low across all age groups (1–44%), with those under 20 particularly lagging (1–4%) as of August 28, 2023 [1,26–28]. These low pediatric vaccination rates, combined with increased social contacts after social distancing measures were lifted, likely contributed to a higher risk from Omicron variants. Our findings indicate that individuals under 20, especially those with vaccine-only immunity, face elevated risks in survival analyses, suggesting that unvaccinated or under-boosted adolescents and their households may significantly contribute to community transmission. [Ref]

Regarding sex-based differences, evidence shows that women are likely at higher risk than men due to both immunological and behavioral factors. Immunologically, women’s stronger immune responses may lead to earlier detection and higher documented case counts [29], and hormone-regulated immune modulation could alter susceptibility and antibody kinetics under Omicron variants [28]. Behaviorally, women often assume primary caregiving roles and are more frequently employed in high-exposure settings (such as education, healthcare, and service sectors), which increases their contact rates and potential for transmission. [REF] Overall, these findings underscore the importance of prioritizing COVID-19 vaccination among vulnerable populations—particularly women—through targeted messaging and strategies. Addressing specific challenges such as elevated contact patterns among women and low pediatric vaccination coverage, while considering the timing of prior vaccination and infection, can improve vaccine uptake and protect these groups more effectively [1].

**Our study has several limitations.** First, numerous factors may affect breakthrough risk [26]. and our observational design precludes full control of unmeasured confounding. Differences in exposure (e.g., occupation, caregiving roles), risk aversion, and healthcare-seeking behavior—all not fully captured—may influence infection outcomes. While these biases could shift our estimates, they do not negate the overall patterns observed, including immunity-, sex- and age-based disparities. Second, the antibody assays used were developed based on the original Wuhan-Hu-1 strain [30], which raises concerns about accurately detecting Omicron-specific S antibodies. Possible misclassification biases include waning antibody levels, varying test sensitivity, and the timing of sampling relative to infection or vaccination. We also measured binding rather than neutralizing antibodies, which may be a less direct indicator of protective immunity. Nonetheless, comparing population-level breakthrough infection rates across hybrid and vaccine-only cohorts, as well as across different sex and age strata, provides valuable insights into real-world immunity trends soon after the Omicron wave. Third, as most of our data were collected during Omicron prevalence, future research should examine whether emerging variants and immune imprinting alter reinfection risk [31]. Expanding these analyses with larger, more granular datasets can help clarify how timing of past infections, booster uptake, sex, and age-specific factors interact to shape COVID-19 risk.

Despite these limitations, the study’s findings have significant implications for public health policy and practice. First, the observed difference between conservative and inclusive infection definitions highlights the importance of broad surveillance methods that capture unconfirmed or asymptomatic infections. In many real-world situations, testing is incomplete, and mild or asymptomatic infections go undiagnosed. By accounting unconfirmed infection into inclusive outcome definition, we capture these hidden cases, leading to a more comprehensive (and higher) risk assessment, allowing more accurate comparisons between groups to determine the high-risk groups especially in hybrid immunity group. This is especially crucial in the context of a highly transmissible virus like Omicron, where many cases may go untested or unreported. Second, although children often display robust antibody responses following infection [32] and generally have lower rates of severe illness [33], our results indicate their growing role in household and community transmission during the Omicron period [34]. Global data also show that pediatric and adolescent infections are rising, driven by relatively lower vaccination coverage and the spread of new variants [34]. As the pandemic evolves—with increasing levels of hybrid immunity and ongoing variant emergence—continued surveillance is crucial for identifying vulnerable groups and assessing wider transmission risks. Public health authorities can more effectively mitigate transmission and protect vulnerable populations by expanding vaccination efforts among females and younger individuals, as well as older adults; accounting for age- and sex-specific exposure and immune response factors with targeted health communication.

**Conclusions**

In summary, this large community-based cohort study compared infection risks associated with different COVID-19 immunity statuses (hybrid and vaccine) after the omicron wave. Comparing conservative and inclusive outcome definitions, the hybrid immunity group exhibited a marked difference, with survival decreasing from 98% to 80%, while the vaccine immunity group showed survival rates from 70% to 60%, respectively, shifting the hazard ratio between the two immunity groups from fivefold to twofold over four months. In hybrid and vaccine immunity groups, females face higher hazard rates than males (31% and 26% higher under the inclusive outcome versus 88% and 25% higher under the conservative outcome). Under the conservative definition, individuals under 20 with vaccine immunity had a 61% higher hazard rate than those aged 40–59, whereas under the inclusive definition, the youngest hybrid immunity group showed a 40% lower hazard rate compared to the same age reference. This suggests that unvaccinated or under-boosted children and adolescents may increasingly contribute to community transmission, especially as new variants emerge. These findings underscore the importance for public health authorities to prioritize COVID-19 vaccination among females and children through targeted campaigns and tailored communication strategies.

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**Appendix**

1. **Pseudo Code of PMM Imputation**

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1. **Cox Proportional Hazard Model Justification**

Fitting the varying coefficient models for both the conservative and inclusive cohorts reveals violations of the proportional hazards (PH) assumption. In the Schoenfeld Residual Test, a p-value < 0.05 indicates a violation of the assumption. For the conservative model, the Immune Type and its interaction with Vaccine Doses show significant violations (p < 0.05). In the inclusive model, the PH assumption is violated for the majority of covariates. As a result, we opted to fit separate models for different immune types and cohorts, ensuring that the proportional hazards (PH) assumption remains valid.A table with numbers and symbols

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Table S1: Schoenfeld Residual Test for Proportional Hazards Assumption in Varying Coefficient Models

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Table S2: Schoenfeld Residual Test for Proportional Hazards Assumption in Immune-Type-Specific Models

1. **Cox Proportional Hazard Model Equations**

The equation below represents the Cox proportional hazards model, describing the hazard rates since the start of surveillance. Here, corresponds to the fitted model for the hybrid-induced group, while represents the model for the vaccine-induced group.

Conservative models:

Inclusive models:

1. **Distributions of Infection Cases by Immune Types and Covariates**

In the table below, confirmed infections and N increase cases are defined according to the conservative and inclusive cohorts outlined in Figure 1. The N increase but not confirmed cases group is a subset of the ‘N increase’ group, excluding individuals with confirmed infections. The proportions are weighted using age-based weights. The bar plot to compare the weighted proportion is shown in Figure S1.



Table S3: Summary table of infection cases distribution