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

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**Abstract**

**Background:** Evaluating the risk of SARS-CoV-2 Omicron and post-Omicron subvariant infections is challenging because many infections remain undetected or unconfirmed. We compared the risks of breakthrough infections caused by these Omicron-lineage variants among individuals with hybrid, vaccine-only, and infection-only immunity in South Korea, incorporating both laboratory-confirmed cases and serology-inferred infections.

**Methods:** Using nationwide surveillance data (August and December 2022), we defined immunity status as hybrid (infection plus vaccination), vaccine-only, and infection-only based on spike (S) and nucleocapsid (N) antibody profiles and vaccination history. Outcomes were analyzed under two definitions: conservative (laboratory-confirmed cases) and inclusive (laboratory-confirmed plus serology-inferred infections signaled by rising N-antibody titers). For unconfirmed events, infection dates were imputed by predictive mean matching, enabling Kaplan–Meier survival curves. Time-varying Cox models produced log hazard ratios (log-HRs).

**Results:** Incorporating serology substantially increased the estimated four-month cumulative infection risk compared with using confirmed cases alone. The hybrid group rose from 2% to 20%, the infection-only group from 4% to 24%, and the vaccine-only group from 30% to 40%. With these additional infections included, the relative advantage of hybrid immunity narrowed. Under the conservative definition, log-HRs comparing hybrid to vaccine-only decreased from 4.10 to 2.34, and hybrid to infection-only decreased from 1.56 to 0.31. Under the inclusive definition, the vaccine-only log-HR declined from 3.44 to 0.13, and the infection-only log-HR shifted from 3.31 to –0.56, indicating greater protection in the infection-only group by month four.

**Conclusions:** Since laboratory-confirmed cases primarily reflect symptomatic disease, vaccination appears to confer added protection against severe infection, yet this benefit fades within a few months. The rapid decline of hybrid immunity and the high burden of unconfirmed infections underscore the need for routine serological monitoring to curb silent transmission and for timely booster campaigns to prevent severe infections in Omicron-driven epidemics.

**Introduction**

Both natural SARS-CoV-2 infection and COVID-19 vaccination jointly shape 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—acquired through both infection and vaccination—provides the highest magnitude and durability of protection across outcomes[6]. A recent study found that hybrid immunity, especially with booster vaccination, provided the strongest protection against SARS-CoV-2 reinfection—reducing risk by up to 57% compared to natural immunity alone and by 65% compared to complete vaccination alone—with effectiveness highest shortly after boosting and gradually waning over time [7,8]. This evidence underscores the importance of vaccinating previously infected individuals, as infection-induced protection against reinfection wanes rapidly while vaccination further strengthens and prolongs immunity [3,4].

However, the widespread rise of the Omicron (B.1.1.529) variant, which has led many individuals to possess hybrid immunity, complicates efforts to measure and compare this protection. While hybrid immunity generally offers strong protection during the Omicron period, its durability varies across studies and populations [ref]. Variations in infection timing, vaccine dosages, and the rise of immune-evasive variants create additional challenges in accurately quantifying the extent and durability of protection[5]. 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[12–14]. 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 immunity groups, respectively [15].

The nationwide Korea Seroprevalence Study of Monitoring of SARS-CoV-2 Antibody Retention and Transmission (K-SEROSMART) was launched in August 2022, to examine the extent of COVID-19 infections— including unconfirmed cases detected by anti-N serology —across local communities through longitudinal cohort surveillance [3]. Baseline findings revealed that most individuals had SARS-CoV-2 antibodies and uncovered a substantial number of previously undetected cases. Our study compared the risks of breakthrough infections caused by these Omicron-lineage variants among individuals with hybrid, vaccine-only, and infection-only immunity in South Korea, incorporating both laboratory-confirmed cases and serology-inferred infections. By shedding light on which populations are most susceptible to breakthrough infections and the relative risk and durability of hybrid, vaccine and infection-induced protection, these findings provide valuable evidence for tailoring targeted interventions and optimizing long-term immunization strategies in diverse community settings.

**Methods**

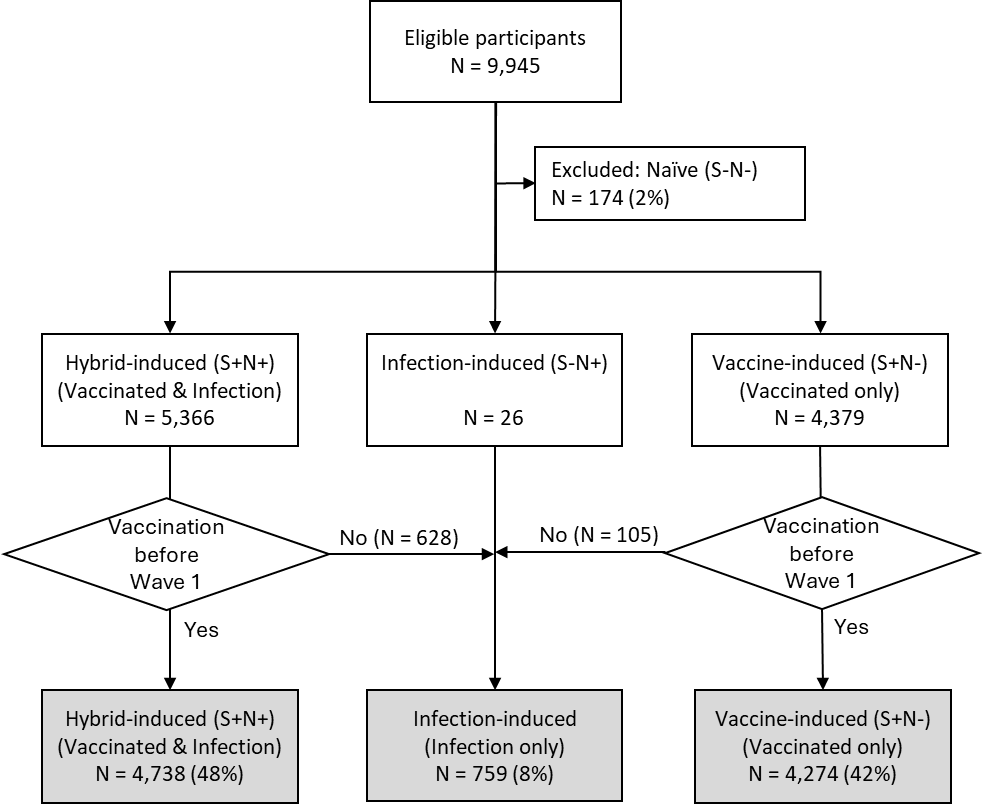
**Participants.** K-SEROSMART Wave 1 fieldwork, conducted from August 12 to September 5, 2022, enrolled 9,945 individuals from 5,041 households in 258 communities across South Korea via a stratified, community-based two-stage random sampling. Recruitment used a staged approach: email/MMS invitations for web surveys, followed by telephone follow-ups for non-respondents, and finally face-to-face home visits[ref] During face-to-face household interviews, participants reported health, demographic, and socioeconomic data and provided blood samples at nearby health centers or clinics. Samples were transported to regional labs on the collection day, and refrigerated before transport to a central laboratory. Four months later, in Dec 2022, the subsequent second survey (Wave 2) revisited the same cohort—shortly after the Omicron BA.5 summer peak—to track shifts in immunity, reinfection rates, and COVID‑19 vaccine effectiveness. December was chosen because a mild winter resurgence driven by BA.5 sub‑lineages BF.7 and BQ.1 coincided with rollout of Korea’s bivalent booster, offering an ideal window to observe short‑term antibody dynamics and community reinfections [16]. Of 8,826 eligible individuals, 7,528 completed Wave 2. Sampling procedures and laboratory testing protocols for the serological assays used in this study are described in detail in a prior publication [17]. All public health centers and medical institutions in Korea are required to report the results of rapid antigen tests and reverse transcription polymerase chain reaction (RT-PCR) screening tests for newly confirmed COVID-19 cases to the COVID-19 information management system of the Korea Disease Control and Prevention Agency (KDCA) within 24 hours. For consenting participants, identifiers (name, sex, birth date, home address) linked survey responses to KDCA records of confirmed infections and vaccination history [17].

**Sample collection and cohort definitions.** For all participants, 4 mL of whole blood was collected and centrifuged at 3,000 rpm for 10 minutes to isolate serum. The serum samples were subsequently analyzed for SARS-CoV-2 antibodies using the Roche Elecsys Anti-SARS-CoV-2 S (Spike) and Anti-SARS-CoV-2 (Nucleocapsid) assays. These assays utilize electrochemiluminescence immunoassay (ECLIA) technology for high-sensitivity detection. The anti-S assay provides a quantitative measure of antibodies against the spike protein receptor-binding domain, while the anti-N assay provides a qualitative detection of antibodies against the nucleocapsid protein. Anti-S results were numerical and classified as positive (reactive) if the titer was ≥0.80$ U/mL, in accordance with the manufacturer's instructions for the Roche Elecsys Anti-SARS-CoV-2 S assay [ref]. This cutoff is established to differentiate true antibody presence from background noise with high specificity.[18]. Anti-N assay results were classified as non-reactive or reactive, using a cut-off index of ≥ 1.0 for reactivity. A reactive result indicates the presence of anti-N antibodies formed from a prior natural infection.[18]. The cohort was divided into four immunity types: hybrid-induced (S+N+ with vaccination), vaccine-induced (S+N− with vaccination), infection-only (S−N+, S+N−, or S+N+ without vaccination), and naive (S−N−) [19,20] (Figure 1). After the Omicron wave in South Korea, 90% had hybrid or vaccine-induced immunity, 8% infection-induced, and 2% no immunity as of August 2022.

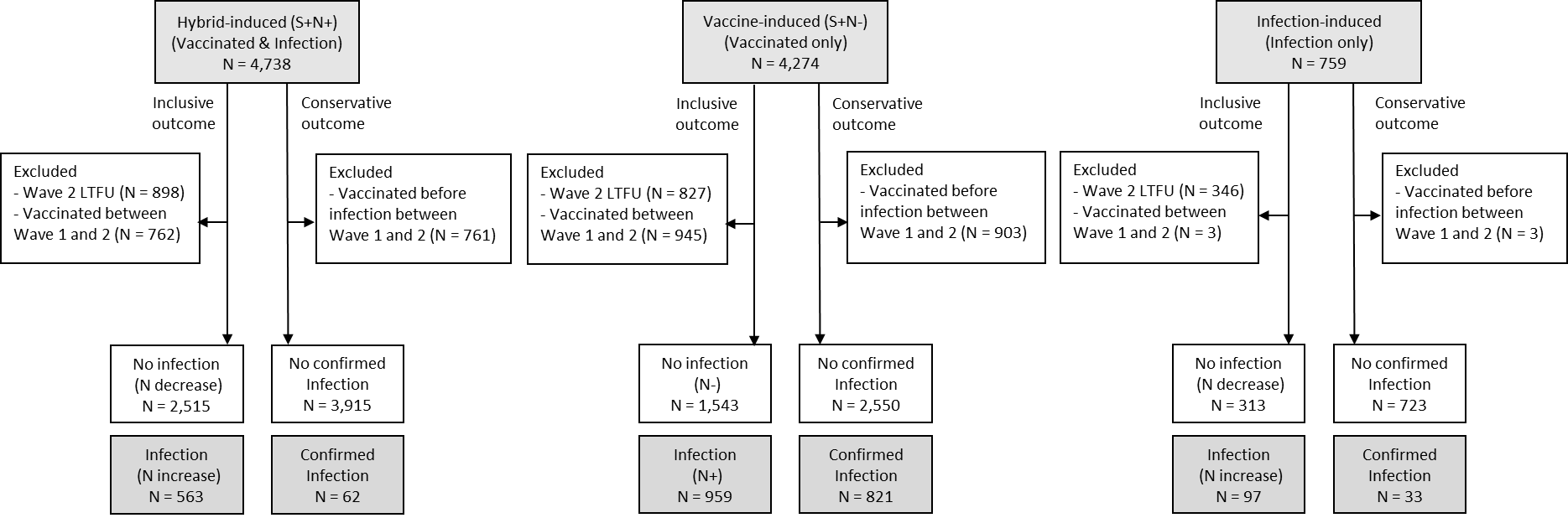
**COVID-19 infection outcomes:**We evaluated two outcome types: 1) conservative outcomes (laboratory confirmed infections) and 2) inclusive outcomes (confirmed and unconfirmed infections) between K-SEROSMART Waves 1 and 2. Confirmed infections were identified through positive test results recorded in the KDCA database. Unconfirmed infections, without a corresponding COVID-19 diagnosis in KDCA records, were stratified by baseline immunity status to account for pre-existing antibodies. 1) Vaccine-Induced Immunity Group (Baseline N-negative): Since these individuals possessed no nucleocapsid antibodies at baseline (Wave 1), any detection of anti-N antibodies at follow-up constitutes a de novo infection event. Therefore, unconfirmed infections in this group were defined as a qualitative seroconversion from non-reactive (Wave 1) to reactive (Wave 2) status based on the manufacturer’s assay cutoff. 2) Hybrid- and Infection-Induced Immunity Groups (Baseline N-positive): Because these participants had pre-existing anti-N antibodies, qualitative seropositivity at Wave 2 captures both past and recent infections. To isolate new infections, we utilized a quantitative definition based on the ratio of titers between Wave 2 and Wave 1. To determine a valid cut-off for this ratio, we performed a validation analysis using the subset of participants with PCR-confirmed breakthrough infections between waves as 'positive controls.' We selected a fold-change threshold that achieved a sensitivity >80% and specificity >90% (Figure S1). This rigorous threshold (where N2/N1 > 1) was chosen specifically to maintain a false-positive rate below 10%, ensuring that minor titer fluctuations due to assay variability were not misclassified as new infections.

Figure 1: Cohort Classification and Outcome Determination Based on Vaccination and Infection Status, using data from K-SEROSMART Waves 1 and 2, and KDCA from August 2022 to December 2022

1. Cohort classification



B. Inclusive and conservative outcome definitions



To ensure the validity of our assessment of infection risk differences by immunity status at Wave 1, we applied the following exclusion criteria: First, for conservative outcome definition, we excluded participants vaccinated before confirmed infections (e.g., N=761, hybrid group) based on the exact timing of vaccination and confirmed infection from the KDCA database. We included those with confirmed infection records from the KDCA database (e.g., N=62 for the hybrid-induced group) between Waves 1 and 2, regardless of participation in Wave 2. Second, for the inclusive outcome definition, we excluded those who did not participate in Wave 2 (e.g. loss to follow up, N=898 for the hybrid induced group) because their change in anti-N status could not be assessed. We also excluded participants who received any vaccination during the interval between Waves 1 and 2, as vaccination alters antibody profiles, and the exact timing of unconfirmed infection is unknown (e.g. N=762 for the hybrid induced group).

**Statistical analysis**. We performed survival analyses for conservative and inclusive outcomes across three immunity groups. Missing infection dates for unconfirmed cases were multiply imputed under the missing-at-random assumption using the {mice} R package with predictive mean matching (PMM). [21]. Dates were expressed as time gaps from the first surveillance, with epidemic-wave indicators to preserve calendar-time structure. Gaps for confirmed cases were estimated from a regression model with demographic (age, sex), clinical (vaccine doses, comorbidities, time since last immunological event), and serological variables (anti-S, anti-N levels). Donor pools were stratified by age and vaccination status, and PMM sampled from the 5–10 nearest neighbors to retain variability and avoid over-smoothing [22]. Fifty imputations were generated, incorporating all covariates from the survival model. Imputed and observed dates showed similar epidemic timing, and delta-adjusted shifts of ±14 days confirmed robustness. Survival probabilities were compared across hybrid, vaccine-induced, and infection-induced groups using age-standardized Kaplan–Meier curves (Figure 2).

We used a time-varying Cox model with log-transformed time interactions because Schoenfeld residual tests indicated proportional hazards violations in both the conservative and inclusive cohorts, rendering the standard model unsuitable. (Table S1 and S2). Vaccine- and infection-induced immunity effects were modeled as functions of log(time), allowing HRs to vary continuously while maintaining interpretability[23,24]. Log-transformed time effectively captured gradual changes in covariate effects[25]. Similar approaches have modeled time-varying effects in epidemiological studies[26,27], providing flexibility for non-proportional hazards. We fitted a full model with age, sex, and BMI, but only age and sex were significant. Time since the last immunological event was excluded due to missing prior infection dates in the infection-induced group. Comorbidity burden was not significantly associated with infection risk and was excluded from final models. The final model is specified as follows. Let denote time in months and let represent the hazard function at time . The baseline hazard function is denoted by . The covariates and are binary indicators for vaccine-induced and infection-induced immunity, respectively, with hybrid-induced immunity serving as the reference category. Age and sex are similarly included as categorical indicator variables. The hazard function is expressed as:

To validate the time-varying Cox model, we conducted a landmark analysis, dividing follow-up into monthly intervals to estimate observed HRs (Table S3). This enabled comparison of model-based estimates with empirical trends. Similar strategies have been used in previous studies to assess the adequacy of time-varying effects and support model validation through interval-specific estimates [28,29]. Within each interval, Fisher’s Exact Test evaluated infection risk differences across immunity groups, suitable for binary outcomes and small event counts in later periods.

**Results****.**

Table 1: Descriptive Characteristics of the Study Population by Immunity Type (Hybrid-, Vaccine-, and Infection-induced), August 2022 to December 2022.





Note: The sum of the proportion of the infection-induced group in time since the most recent immunological event is not 100% because some individuals do not have the last confirmed infection records or vaccination records.



Table 1 shows demographic and clinical differences among hybrid-induced (S+N+), vaccine-induced (S+N–), and infection-induced immunity groups. The infection-only group was notably younger (68.2% aged <20 vs. 8.4% hybrid, 5.9% vaccine). Hybrid and infection-only groups had more recent immunological events (74% and 66% within 6 months, vs. 37% vaccine). The hybrid had fewer four dose vaccination before Wave 1 (13% vs. 25% vaccine). Across both outcome definitions, the hybrid group had the lowest infection rates: under the conservative definition, 2% vs. 4% (infection-only) and 21% (vaccine-only); under the inclusive definition, 12% vs. 14% and 24%, respectively.

Table 2: Characteristics of Participants of Breakthrough Infection Events by Immunity Type (Hybrid-, Vaccine-, and Infection-induced) and Outcome Definition (Conservative vs. Inclusive), August 2022 to December 2022

Note: 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. In the hybrid group, 563 participants showed an N-titer rise between Wave 1 and 2; Among these participants, 520 lacked laboratory‑confirmed infection dates, whereas 43 had dates recorded in the KDCA database—forming part of the 62 confirmed cases. The remaining 19 missed Wave 2 but were still counted in the conservative outcome because their infection dates were confirmed in the KDCA database.

Table 2 shows notable differences in the estimated number of unconfirmed infections between conservative and inclusive outcomes across immunity groups. Under the inclusive criteria, the number of potential infections is substantially higher than in the conservative approach (e.g., 563 vs. 62 in the hybrid group; 959 vs. 821 in the vaccine group; 97 vs. 33 in the infection only group), because it includes “N increase/positive but not confirmed” cases. This pattern is further reflected in the confirmation status distribution: 92% (520 out of 563) of infections within the hybrid-induced group not receiving laboratory confirmation, and 81% (79 out of 97) in infection-only group, while 50% (477 out of 959) of infections in the vaccine-induced immunity group.

The discrepancy between conservative and inclusive outcomes stem from the interval since the most recent immunological event and the participants’ age distribution. At Wave 1, the inclusive criteria classified 33 % of hybrid-immunity cases as < 1 month post-immunological event, versus 4 % under the conservative criteria. Similarly, among vaccine-only cases, the inclusive definition captured 19 % that were < 1 month post-immunological event, compared with 5 % under the conservative definition. Anti-N threshold analyses suggest a 10% false-positive error (Figure S1), especially for unconfirmed cases within 1 month post-immunological event with delayed N-titer rise (e.g., 10% of 181 hybrid, 24 infection-only). Age impacts outcomes: adults 40–59 dominate unconfirmed infections in hybrid (37%) and vaccine-only (45%) groups, while those <20 dominate infection-only (69%).

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| Figure 2: Kaplan-Meier Survival Curves by Immunity Type (Hybrid-, Vaccine-, and Infection-induced) and Outcome Definition (Conservative vs. Inclusive), August 2022 to December 2022 | |
| 1. Conservative outcome definitions | 1. Inclusive outcome definitions |
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Figure 2 shows Kaplan-Meier survival curves for remaining COVID-19 infection-free over 4 months between Waves 1 and 2, using conservative (Panel A) and inclusive (Panel B) outcome definitions. It compares hybrid, vaccine, and infection-induced immunity groups. By month 4, the conservative outcome definition yielded infection risks of 2 % (95% CI: 1.3%, 1.9%) for the hybrid-immunity, 4% (95% CI: 2.3%, 5.6%) in the infection only, and 30 % (95% CI: 17.3%, 41.8%) in the vaccine-only; under the inclusive outcome definition, these rose to 20 % (95% CI: 18.1%, 19.9%), 24% (95% CI: 19.6%, 29.1%) and 40 % (95% CI: 36.3%, 43.5%) respectively.

Figure 3: Time-varying Cox Log Hazard Ratios for Vaccine and Infection Only-Immunity Groups Against Hybrid Immunity Group, August 2022 to December 2022

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| --- | --- |
| 1. Conservative outcome definition | 1. Inclusive outcome definition |
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Table 3. Monthly Log HR Estimated from Time-varying Cox Regression for Vaccine and Infection Only-Immunity Groups Against Hybrid Immunity Group, August 2022 to December 2022

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| |  |  |  | | --- | --- | --- | |  | Log-HR (reference: hybrid-induced inmmunity) | | | Time (month) | Vaccine-induced (log HR, 95% CI) | Infection-induced (log HR, 95% CI) | | 0 | 4.10 (2.90, 5.31) | 1.56 (-0.01, 3.13) | | 1 | 3.00 (2.63, 3.38) | 0.78 (2.22, 1.34) | | 2 | 2.67 (2.37, 2.97) | 0.54 (0.01, 1.07) | | 3 | 2.48 (2.12, 2.85) | 0.41 (-0.22, 1.03) | | 4 | 2.34 (1.90, 2.79) | 0.31 (-0.43, 1.04) | | |  |  |  | | --- | --- | --- | |  | Log-HR (reference: hybrid-induced inmmunity) | | | Time (month) | Vaccine-induced (log HR, 95% CI) | Infection-induced (log HR, 95% CI) | | 0 | 4.10 (2.90, 5.31) | 1.56 (-0.01, 3.13) | | 1 | 3.00 (2.63, 3.38) | 0.78 (2.22, 1.34) | | 2 | 2.67 (2.37, 2.97) | 0.54 (0.01, 1.07) | | 3 | 2.48 (2.12, 2.85) | 0.41 (-0.22, 1.03) | | 4 | 2.34 (1.90, 2.79) | 0.31 (-0.43, 1.04) | |

Figure 3 displays time-varying log-HR from Cox regression models, comparing vaccine- and infection-induced immunity to hybrid-induced immunity using log-transformed time interactions. Conservative (Panel a) and inclusive (Panel b) definitions show notable differences in vaccine-induced immunity’s baseline log-HR. As shown in Table 3, under conservative outcomes, hybrid immunity had the lowest log-HR for lab-confirmed COVID-19 over four months. Vaccine-only immunity had the highest excess risk, with log-HR vs. hybrid falling from 4.10 (95% CI: 2.90, 5.31) at baseline to 2.34 (95% CI: 1.90, 2.79) at month 4, remaining significant. Infection-only immunity started at 1.56 (95% CI: –0.01, 3.13), dropping to 0.78 at month 1 and 0.31 by month 4, with confidence intervals overlapping the null from month 3, indicating convergence with hybrid immunity.

Under the inclusive outcome definition, the vaccine-induced group initially showed a higher infection risk, with log-HR of 3.44 (95% CI: 2.81, 4.06) compared to the hybrid-induced immunity group. By month 4, this dropped to 0.13 (95% CI: –0.07, 0.33), indicating near-equal protection. The infection-induced group started with log-HR of 3.31 (95% CI: 2.55, 4.07), but by month 2, it fell below zero, suggesting greater protection than hybrid immunity. By month 4, its confidence interval was –0.56 (95% CI: –0.98, –0.14), showing significant protection. Table S3 confirms these trends, with HRs for hybrid vs. vaccine-induced dropping from 5.64 to 1.33, and hybrid vs. infection-induced from 3.63 to 0.35, indicating hybrid immunity’s advantage wanes over four months. A direct comparison between vaccine-only and infection-only immunity is additionally presented in Figure S1(a)–(b).

**Discussion**

Using nationwide, community‑based surveillance conducted after South Korea’s Omicron wave, we compared infection risks among hybrid, vaccine-only, and infection-only immunity groups. Hybrid immunity showed the lowest log-HR for both inclusive and conservative outcomes over four months. Including unconfirmed infections reduced hybrid immunity’s protective benefit, with infection risk rising from 2% to 20% in the hybrid group, altering comparative HRs. The hybrid vs. vaccine-only log hazard ratio fell from 3.44 to 0.13, and the hybrid vs. infection-only reversed from 3.31 to –0.56 under inclusive outcomes. Under the conservative outcome definition, the log hazard ratio of hybrid vs. vaccine-only immunity dropped from 4.10 to 2.34, and that of hybrid vs. infection-only immunity dropped from 1.56 to 0.31. Since laboratory-confirmed cases primarily reflect symptomatic disease, vaccination appears to confer added protection against severe infection, yet this benefit fades within a few months. The rapid decline of hybrid immunity and the high burden of unconfirmed infections underscore the need for routine serological monitoring to curb silent transmission and for timely booster campaigns to prevent severe infections in Omicron-driven epidemics.

To our knowledge, this study is the first to systematically evaluate efficacy using both conservative (PCR-confirmed) and inclusive (serology-detected) definitions of breakthrough infection. PCR-based outcomes primarily capture protection against symptomatic disease—events critical for healthcare capacity—while serology reveals broader, often undiagnosed infections that better quantify immunity’s role in preventing transmission. Evidence from 2022–2024 [30–33] shows Omicron subvariants (BA.1, BA.2, BA.5) increased mild or asymptomatic breakthroughs, with hybrid immunity providing robust yet time-waning protection, especially against severe disease. Our findings indicate that even remote prior vaccination, combined with hybrid immunity, prevents symptomatic illness effectively, outperforming vaccine-only and infection-only groups for at least four months. This divergence between outcome definitions aligns with known immunological hierarchies. While circulating neutralizing antibodies (NAbs)—the primary barrier against acquisition of infection—decay rapidly within months post-exposure, cellular immunity (T-cell responses which prevent severe disease) remains robust and durable. [ref] This likely explains why hybrid and vaccine-induced immunity continued to provide significant protection against the conservative outcome (symptomatic/severe cases) despite the rapid loss of protection against asymptomatic serological conversion.

Accordingly, our study shows hybrid immunity against all infections declines more quickly, dropping below the infection-only group within 2–4 months. This result aligns with Bobrovitz et al.[6] that the protective advantage of hybrid immunity over infection-only immunity wanes over time, with estimates converging by around 4–6 months. The observation that infection-only immunity eventually appeared more protective than hybrid immunity against serological conversion warrants biological scrutiny. Two mechanisms may contribute. First, natural infection stimulates high levels of secretory IgA in the upper respiratory tract (mucosal immunity), providing a frontline barrier against reinfection that intramuscular vaccination fails to induce efficiently. [ref] Second, hybrid immunity in this cohort relied on vaccines targeting the ancestral Wuhan-Hu-1 strain (Korea **transitioned to Bivalent vaccination from late 2022).** Exposure to Omicron in these individuals effectively boosts high titers of cross-reactive antibodies, but may limit the generation of *de novo* antibodies specific to the divergent Omicron spike (immune imprinting).[ref] Conversely, individuals with infection-only immunity—presumed to be acquired during the recent Omicron wave—may possess a narrower but more precisely matched neutralizing antibody repertoire against the circulating variant, potentially explaining their sustained resistance to reinfection relative to the hybrid group in the later months.

Our study employs a robust approach to quantify and compare infection risks across immunity groups by estimating infection timing (via PMM) for survival analysis and quantifying uncertainty around N-antibody titer thresholds to define infections. We applied a time-varying Cox proportional hazards model to mitigate survival bias in calendar-time follow-up. Yet, residual survival bias may persist due to unequal times since the last immunological event. At baseline, time-varying HRs show higher infection risks in the vaccine-only group, likely due to the majority of their last immune event occurring ≥6 months prior, leading to antibody titer decline against Omicron sub-variants. This bias likely underestimates later risks in the vaccine-only group, as higher early hazards in the vaccine-only group disproportionately remove highly susceptible individuals (who are likely older population and with a longer time since the last immunological event), leaving a less susceptible "survivor" subset. This narrows the apparent risk gap with the hybrid immunity group, even if underlying protection is not truly superior, emphasizing the need for timely boosters and non-pharmaceutical precautions in this group. The infection-only group, despite the majority of <6-month immune event gaps, also has elevated initial risk, suggesting qualitative differences in protection beyond timing. Natural infection may induce a broader but less consistent immune response compared to vaccines, influenced by infecting strain, disease severity, and host factors, potentially resulting in weaker or narrower immunity in some individuals, increasing early reinfection risk **[34,35]. Nevertheless, our findings remain robust, showing that hybrid immunity offers the strongest initial protection but wanes quickly—approaching the vaccine-only group and falling below the infection-only group by month four under the inclusive definition. These patterns underscore the need for timely boosters, especially for individuals whose last immune event occurred several months earlier and suggest that previously infected populations may benefit from targeted booster prioritization to maintain population-level protection against emerging variants.**

**Our study has some limitations. First, lacking symptom-level data for Waves 1 and 2, we treated infection as a binary event, unable to assess if hybrid, vaccine-only, or infection-only immunity differently protects against severe COVID-19. Future studies should combine N-antibody surveillance with clinical endpoints (symptom severity, hospitalization) to evaluate waning patterns for severe outcomes, refining booster timing. Second, the loss to follow-up in Wave 2 (19%, 19%, and 46% for the hybrid, vaccine, and infection groups, respectively) for the inclusive outcome may slightly bias the estimated infection risks. While only a small proportion of those lost to follow-up (2%, 22%, and 2% for the hybrid, vaccine, and infection groups) were confirmed infected in the KDCA database, their true infection status cannot be fully determined. Assuming random loss to follow-up with similar underlying risk across immunity groups, our key finding remains unchanged: hybrid immunity shows the highest—but steadily declining—risk relative to other groups when infections are defined inclusively rather than conservatively. Third, Anti-N assays based on the Wuhan-Hu-1 antigen may under-detect Omicron infections, waning titers and sampling timing further compound misclassification. Although our sensitivity analyses confirmed robust N titer cut off for infection outcome in hybrid and infection-only groups, very recent infections (≤1 month) were under-powered, possibly obscuring delayed seroconversion.** Additionally, our reliance on a significant rise in anti-N titers to identify unconfirmed infections does not account for the antibody 'ceiling effect.' Individuals with high baseline anti-N titers—most common in the hybrid and infection-only groups due to recent prior exposure—may not exhibit a statistically significant titer increase following reinfection due to assay saturation or biological limits on antibody production. Consequently, this method may underestimate the true incidence of breakthrough infections (inclusive outcome) in groups with pre-existing natural immunity, potentially biasing the hazard ratios to appear more protective than they are.  **Larger cohorts, stratified by infection recency, and vaccination status, are needed to refine N titer thresholds, especially in pediatric and older adults. Fourth, Anti-N identifies exposure but not protective immunity; S-titer better predicts risk via neutralizing capacity. Our reliance on N-titer alone limited our ability to assess functional protection. Future studies with larger sample size could stratify individuals by S-titer levels (high, medium, low) based on protective thresholds derived from neutralization studies or incorporate additional markers such as mucosal IgA and SARS-CoV-2-specific T-cell assays to distinguish immune imprinting—where prior exposure biases responses toward ancestral epitopes—from recent Omicron exposure.** Such multi-analyte profiling could clarify whether the rapid decline in immunity is driven by biological factors (e.g., waning kinetics, immune imprinting) or behavioral factors (e.g., differential exposure, testing-seeking practices), informing targeted vaccination and surveillance strategies. **Finally, unmeasured confounders (e.g., occupation, healthcare-seeking behavior) may affect breakthrough infection estimates. Nevertheless, by integrating quantitative serology with registry data, our study quantified the relative risk and durability of hybrid, vaccine‑only, and infection‑only immunity and identified groups vulnerable to silent infection and targeted for timely booster campaigns.**

**Conclusions**

K-SEROSMART surveillance post-South Korea’s Omicron wave shows that hybrid immunity’s initial lower infection risk fades when including anti-N-detected, unreported infections. Inclusive definitions raise risk estimates: hybrid from 2% to 20%, infection-only from 4% to 24%, vaccine-only from 30% to 40%, compared to conservative definitions. Hybrid immunity’s advantage wanes under inclusive definitions, with vaccine-induced log hazard ratio dropping from 3.44 to 0.13 and infection-induced from 3.31 to –0.56 by month 4. High unconfirmed infection rates (92% hybrid, 50% vaccine-only, 81% infection-only) reveal surveillance gaps skewing protection comparisons. The rapid decline of hybrid immunity and the high burden of unconfirmed infections underscore the need for routine serological monitoring to curb silent transmission and for timely booster campaigns to prevent severe infections in Omicron-driven epidemics.

**List of abbreviations**

* Anti-N – Anti-nucleocapsid protein
* Anti-S – Anti-spike protein
* CI – Confidence interval
* COVID-19 – Coronavirus disease 2019
* HR – Hazard ratio
* K-SEROSMART – Korea Seroprevalence Study of Monitoring of SARS-CoV-2 Antibody Retention and Transmission
* KDCA – Korea Disease Control and Prevention Agency
* SARS-CoV-2 – Severe acute respiratory syndrome coronavirus 2

**Declarations**

**Ethical approval and consent to participate**

The Institutional Review Board of the KDCA exempted this survey from review, in accordance with Article 36 of the Bioethics Act, Article 33 of the Enforcement Rules, and Article 2 of the Bioethics Act. The study was deemed necessary for urgent public health action and was conducted directly or commissioned by the state or local government to review and evaluate public welfare or service programs (2022-11-02-PE-A). All participants provided informed consent.

**Consent for publication**

Not applicable.

**Availability of data and materials**

All the processed data and code can be found at GitHub Link: https://github.com/UConn-Health-Disease-Modeling/2023\_South\_Korea\_Seroprevalence.git

**Competing Interests**

The authors declare that they have no competing interests.

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**Author Contributions**

DHK, YJJ, YZ, and WC conceptualized the study. YZ performed the data analysis and visualization. YZ and YJJ completed the first draft of the manuscript. DHK and SJ had directly accessed and verified the underlying data. KD, SJ, WC, JJ, KRP, and DHK interpreted the results and critically revised the manuscript. DHK supervised the project administration. DHK, YJJ, YZ, JJ, and SJ had full access to all the data in the study and accepted responsibility to submit for publication. All authors read and approved the submitted version.

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# **Figure Legends**

Figure 1. Cohort classification and outcome determination

Panel A shows the conservative outcome definition based on laboratory-confirmed infections.

Panel B shows the inclusive outcome definition incorporating both confirmed and serology-inferred infections.

The figure summarizes immunity-group classification (hybrid, vaccine-only, infection-only, naïve) from K-SEROSMART Waves 1 and 2 and how infection events were determined through KDCA reporting and anti-N antibody changes.

Figure 2. Kaplan–Meier curves for remaining infection-free by immunity type

Panel A displays age-standardized survival curves under the conservative definition (confirmed infections only).

Panel B shows the inclusive definition incorporating serology-inferred infections.

Across both definitions, hybrid immunity demonstrates the lowest cumulative infection risk, while vaccine-only immunity shows the highest.

Figure 3. Time-varying Cox log hazard ratios by immunity type

Panel A shows time-varying log hazard ratios under the conservative outcome definition.

Panel B shows the inclusive definition including serology-inferred infections.

Vaccine- and infection-induced immunity are compared against the hybrid group, illustrating how relative protection changes over the four-month follow-up period.

# **Tables**

Table 1: Descriptive Characteristics of the Study Population by Immunity Type (Hybrid-, Vaccine-, and Infection-induced), August 2022 to December 2022.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Characteristics** | | **TOTAL** | | | **Hybrid-induced (S+N+)** | | | **Vaccine-induced (S+N-)** | | | **Infection-induced** | | |
| **Num** | **%** | **Weighted (%)** | **Num** | **%** | **Weighted (%)** | **Num** | **%** | **Weighted (%)** | **Num** | **%** | **Weighted (%)** |
| 9,771 | ̵ | ̵ | 4,738 | ̵ | ̵ | 4,274 | ̵ | ̵ | 759 | ̵ | ̵ |
| **Age** | **<20** | 958 | 9.8 | 12.8 | 308 | 6.5 | 8.4 | 181 | 4.2 | 5.9 | 469 | 61.8 | 68.2 |
| **20-40** | 1,934 | 19.8 | 28.4 | 1,127 | 23.8 | 32.5 | 717 | 16.8 | 26.3 | 90 | 11.9 | 14.9 |
| **40-60** | 3,008 | 30.8 | 33.2 | 1,660 | 35.0 | 36.8 | 1,281 | 30.0 | 34.4 | 67 | 8.8 | 8.5 |
| **>60** | 3,871 | 39.6 | 25.6 | 1,643 | 34.7 | 22.3 | 2,095 | 49.0 | 33.3 | 133 | 17.5 | 8.3 |
| **Sex** | **Male** | 4,381 | 44.8 | 49.7 | 2,081 | 43.9 | 49.2 | 1,952 | 45.7 | 50.1 | 348 | 45.8 | 50.2 |
| **Female** | 5,390 | 55.2 | 50.3 | 2,657 | 56.1 | 50.8 | 2,322 | 54.3 | 49.9 | 411 | 54.2 | 49.8 |
| **BMI** | **Low** | 718 | 7.3 | 8.5 | 234 | 4.9 | 5.5 | 234 | 5.5 | 5.9 | 250 | 32.9 | 35.8 |
| **Normal** | 6,046 | 61.9 | 60.4 | 2,994 | 63.2 | 62.3 | 2,667 | 62.4 | 60.5 | 385 | 50.7 | 49.5 |
| **Obesity** | 2,866 | 29.3 | 29.4 | 1,438 | 30.4 | 30.3 | 1,314 | 30.7 | 31.9 | 114 | 15.0 | 13 |
| **Number of underlying disease conditions** | **None** | 5,811 | 59.5 | 68.6 | 2,966 | 62.6 | 70.6 | 2,230 | 52.2 | 61.7 | 615 | 81.0 | 88.7 |
| **1** | 1,860 | 19.0 | 15.6 | 857 | 18.1 | 14.8 | 933 | 21.8 | 18.5 | 70 | 9.2 | 6.6 |
| **2** | 1,246 | 12.8 | 9.6 | 566 | 11.9 | 9.1 | 641 | 15.0 | 11.7 | 39 | 5.1 | 2.5 |
| **>=3** | 854 | 8.7 | 6.2 | 349 | 7.4 | 5.4 | 470 | 11.0 | 8.1 | 35 | 4.6 | 2.1 |
| **Time since the most recent immunological event** | **<1 month** | 1,123 | 11.5 | 10.7 | 575 | 12.1 | 11.2 | 502 | 11.7 | 11 | 46 | 6.1 | 6.9 |
| **1-6 months** | 4,857 | 49.7 | 47.6 | 3,045 | 64.3 | 63.6 | 1,404 | 32.8 | 25.6 | 408 | 53.8 | 58.8 |
| **6-12 months** | 3,498 | 35.8 | 38.9 | 1,112 | 23.5 | 25.1 | 2,348 | 54.9 | 63 | 38 | 5.0 | 6.3 |
| **>1 year** | 26 | 0.3 | 0.3 | 6 | 0.1 | 0.1 | 20 | 0.5 | 0.5 | - | - | - |
| **Vaccination (before the Wave 1)** | **No Vaccination** | 759 | 7.8 | 9.1 | - | - | - | - | - | - | 759 | 100.0 | 100 |
| **Primary Series** | 1,568 | 16.0 | 20.6 | 1,016 | 21.4 | 26.9 | 552 | 12.9 | 17.5 | - | - | - |
| **3 doses** | 5,008 | 51.3 | 53.7 | 2,784 | 58.8 | 60.2 | 2,224 | 52.0 | 57.8 | - | - | - |
| **4 doses** | 2,436 | 24.9 | 16.5 | 938 | 19.8 | 12.9 | 1,498 | 35.0 | 24.7 | - | - | - |
| **Events between the Wave 1 and 2** | **Infection (N positive/increase)** | 1,619 | 16.6 | 16.9 | 563 | 11.9 | 12 | 959 | 22.4 | 23.6 | 97 | 12.8 | 14 |
| **No Infection** | 4,371 | 44.7 | 47.6 | 2,515 | 53.1 | 55.4 | 1,543 | 36.1 | 38.3 | 313 | 41.2 | 46.1 |
| **Loss to follow up in Wave 2** | 2,071 | 21.2 | 22.9 | 898 | 19.0 | 21 | 827 | 19.3 | 21.6 | 346 | 45.6 | 39.4 |
| **Vaccination (from KDCA)** | 1,710 | 17.5 | 12.6 | 762 | 16.1 | 11.6 | 945 | 22.1 | 16.4 | 3 | 0.4 | 0.5 |
| **Confirmed infection (from KDCA)** | 916 | 9.4 | 9.6 | 62 | 1.3 | 1.5 | 821 | 19.2 | 20.7 | 33 | 4.3 | 3.9 |
| **No confirmed infection (from KDCA)** | 7,188 | 73.6 | 78.1 | 3,915 | 82.6 | 86.9 | 2,550 | 59.7 | 63.6 | 723 | 95.3 | 95.6 |

Note: The sum of the proportion of the infection-induced group in time since the most recent immunological event is not 100% because some individuals do not have the last confirmed infection records or vaccination records.



Table 2: Characteristics of Participants of Breakthrough Infection Events by Immunity Type (Hybrid-, Vaccine-, and Infection-induced) and Outcome Definition (Conservative vs. Inclusive), August 2022 to December 2022

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Total population** | | **Hybrid-induced (S+N+)** | | | | | | | | **Vaccine-induced (S+N-)** | | | | | | | | | **Infection-induced** | | | | | | | | |
| **Conservative** | | **Inclusive** | | | **N increase but not confirmed** | | | **Conservative** | | | **Inclusive** | | | **N positive but not confirmed** | | | **Conservative** | | | **Inclusive** | | | **N increase but not confirmed** | | |
| **Confirmed Infection** | | **N increase** | | | **Confirmed Infection** | | | **N positive** | | | **Confirmed Infection** | | | **N increase** | | |
| **Total** | | 62 | - | | 563 | - | | 520 | - | | 821 | - | | 959 | - | | 477 | - | | 33 | - | | 97 | - | | 79 | - | |
| **Age** | **<20** | 6 | (14%) | | 22 | (5%) | | 18 | (4%) | | 59 | (9%) | | 60 | (8%) | | 15 | (5%) | | 26 | (77%) | | 69 | (72%) | | 53 | (69%) | |
| **20-39** | 13 | (30%) | | 146 | (34%) | | 139 | (36%) | | 155 | (27%) | | 158 | (24%) | | 60 | (22%) | | 2 | (11%) | | 17 | (20%) | | 16 | (22%) | |
| **40-59** | 23 | (42%) | | 216 | (38%) | | 197 | (37%) | | 262 | (36%) | | 352 | (40%) | | 171 | (45%) | | 2 | (7%) | | 7 | (7%) | | 6 | (7%) | |
| **≥60** | 20 | (15%) | | 179 | (22%) | | 166 | (23%) | | 345 | (28%) | | 389 | (28%) | | 177 | (29%) | | 3 | (6%) | | 4 | (2%) | | 4 | (2%) | |
| **Sex** | **Male** | 18 | (39%) | | 206 | (41%) | | 195 | (42%) | | 327 | (46%) | | 375 | (44%) | | 169 | (43%) | | 14 | (42%) | | 44 | (49%) | | 36 | (50%) | |
| **Female** | 44 | (61%) | | 357 | (59%) | | 325 | (58%) | | 494 | (54%) | | 584 | (56%) | | 254 | (57%) | | 19 | (59%) | | 53 | (51%) | | 43 | (50%) | |
| **BMI** | **Low** | 5 | (10%) | | 29 | (6%) | | 25 | (6%) | | 58 | (8%) | | 60 | (7%) | | 18 | (5%) | | 12 | (38%) | | 40 | (42%) | | 32 | (42%) | |
| **Normal** | 39 | (59%) | | 371 | (64%) | | 341 | (64%) | | 506 | (59%) | | 610 | (61%) | | 279 | (64%) | | 15 | (47%) | | 44 | (46%) | | 38 | (47%) | |
| **Obesity** | 17 | (30%) | | 155 | (28%) | | 146 | (28%) | | 250 | (32%) | | 279 | (31%) | | 121 | (29%) | | 6 | (16%) | | 13 | (12%) | | 9 | (10%) | |
| **Number of underlying disease conditions** | **None** | 41 | (78%) | | 359 | (71%) | | 329 | (71%) | | 472 | (67%) | | 566 | (66%) | | 240 | (62%) | | 28 | (89%) | | 88 | (93%) | | 71 | (93%) | |
| **1** | 10 | (11%) | | 103 | (15%) | | 97 | (15%) | | 166 | (18%) | | 199 | (18%) | | 97 | (19%) | | 3 | (7%) | | 8 | (7%) | | 7 | (7%) | |
| **2** | 8 | (8%) | | 67 | (10%) | | 63 | (10%) | | 106 | (9%) | | 112 | (10%) | | 47 | (10%) | | 1 | (2%) | | 1 | (0%) | | 1 | (0%) | |
| **≥3** | 3 | (2%) | | 34 | (4%) | | 31 | (4%) | | 77 | (6%) | | 82 | (6%) | | 39 | (8%) | | 1 | (2%) | | - | - | | - | - | |
| **Time since the most recent immunological event** | **< 1 month** | 4 | (4%) | | 183 | (33%) | | 181 | (35%) | | 48 | (5%) | | 187 | (19%) | | 153 | (39%) | | - | - | | 24 | (27%) | | 24 | (32%) | |
| **1-6 months** | 46 | (74%) | | 254 | (46%) | | 221 | (43%) | | 234 | (23%) | | 209 | (18%) | | 72 | (12%) | | 27 | (85%) | | 54 | (57%) | | 37 | (50%) | |
| **6-12 months** | 12 | (23%) | | 124 | (21%) | | 116 | (21%) | | 534 | (72%) | | 560 | (63%) | | 198 | (48%) | | 1 | (2%) | | 7 | (8%) | | 7 | (9%) | |
| **> 1 year** | - | (0%) | | 2 | (1%) | | 2 | (1%) | | 5 | (1%) | | 3 | (1%) | | - | - | | - | - | | - | - | | - | - | |
| **Vaccination (before the Wave 1)** | **No Vaccination** | - | - | | - | - | | - | - | | - | - | | - | - | | - | - | | 33 | (100%) | | 97 | (100%) | | 79 | (100%) | |
| **Primary Series** | 13 | (31%) | | 109 | (24%) | | 103 | (24%) | | 140 | (22%) | | 141 | (19%) | | 48 | (14%) | | - | - | | - | - | | - | - | |
| **3 doses** | 34 | (58%) | | 368 | (65%) | | 341 | (65%) | | 450 | (59%) | | 582 | (64%) | | 277 | (70%) | | - | - | | - | - | | - | - | |
| **4 doses** | 15 | (11%) | | 86 | (11%) | | 76 | (11%) | | 231 | (19%) | | 236 | (17%) | | 98 | (16%) | | - | - | | - | - | | - | - | |

Note: 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. In the hybrid group, 563 participants showed an N-titer rise between Wave 1 and 2; Among these participants, 520 lacked laboratory‑confirmed infection dates, whereas 43 had dates recorded in the KDCA database—forming part of the 62 confirmed cases. The remaining 19 missed Wave 2 but were still counted in the conservative outcome because their infection dates were confirmed in the KDCA database.

|  |  |
| --- | --- |
| Table 3. Monthly Log HR Estimated from Time-varying Cox Regression for Vaccine and Infection Only-Immunity Groups Against Hybrid Immunity Group, August 2022 to December 2022 | |
| 1. Conservative outcome definition  |  |  |  | | --- | --- | --- | |  | Log-HR (reference: hybrid-induced inmmunity) | | | Time (month) | Vaccine-induced (log HR, 95% CI) | Infection-induced (log HR, 95% CI) | | 0 | 4.10 (2.90, 5.31) | 1.56 (-0.01, 3.13) | | 1 | 3.00 (2.63, 3.38) | 0.78 (2.22, 1.34) | | 2 | 2.67 (2.37, 2.97) | 0.54 (0.01, 1.07) | | 3 | 2.48 (2.12, 2.85) | 0.41 (-0.22, 1.03) | | 4 | 2.34 (1.90, 2.79) | 0.31 (-0.43, 1.04) | | 1. Inclusive outcome definition  |  |  |  | | --- | --- | --- | |  | Log-HR (reference: hybrid-induced inmmunity) | | | Time (month) | Vaccine-induced (log HR, 95% CI) | Infection-induced (log HR, 95% CI) | | 0 | 3.44 (2.81, 4.06) | 3.31 (2.55, 4.07) | | 1 | 1.37 (1.19, 1.55) | 0.89 (0.57, 1.21) | | 2 | 0.75 (0.62, 0.87) | 0.16 (-0.16, 0.48) | | 3 | 0.38 (0.22, 0.54) | -0.26 (-0.64, 0.11) | | 4 | 0.13 (-0.07, 0.33) | -0.56 (-0.98, 0.14) | |