Clinical and laboratory considerations: Determining an antibody-based composite correlate of risk for reinfection with SARS-CoV-2 or severe COVID-19

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Abstract

Much of the global population now has some level of adaptive immunity to SARS-CoV-2 induced by exposure to the virus (natural infection), vaccination, or a combination of both (hybrid immunity). Key questions that subsequently arise relate to the duration and the level of protection an individual might expect based on their infection and vaccination history. A multi-component composite correlate of risk (CoR) could inform individuals and stakeholders about protection and aid decision making. This perspective evaluates the various elements that need to be accommodated in the development of an antibody-based composite CoR for reinfection with SARS-CoV-2 or development of severe COVID-19, including variation in exposure dose, transmission route, viral genetic variation, patient factors, and vaccination status. We provide an overview of antibody dynamics to aid exploration of the specifics of SARS-CoV-2 antibody testing. We further discuss anti-SARS-CoV-2 immunoassays, sample matrices, testing formats, frequency of sampling and the optimal time point for such sampling. Whilst the development of a composite CoR is challenging, we provide our recommendations for each of these key areas and highlight areas that require further work to be undertaken.

Introduction

The COVID-19 pandemic, caused by severe acute respiratory coronavirus 2 (SARS-CoV-2) led to unprecedented, accelerated vaccine development (1) and expansive roll-out programs (2,3). Much of the global population now has some level of adaptive immunity to SARS-CoV-2 induced by exposure to the virus (natural infection), vaccination, or a combination of both (hybrid immunity).

Natural infection induced by, and/or vaccination against, SARS-CoV-2 leads to the development of both binding and neutralizing antibodies (nAbs) (4,5), and the induction of T-cell responses during active immune reaction and clearance of infection (6). Key questions that subsequently arise relate to the duration and the level of protection an individual might expect based on their infection and vaccination history. Studies of those infected early in the pandemic documented that natural SARS-CoV-2 infection afforded some level of protection against reinfection in most individuals, and that subsequent reinfections were typically less severe than the primary episode (**Table 1**). However, SARS-CoV-2 has high rates of mutation and heavily mutated variants have emerged (7). Most significant are the 'variants of concern' (VOCs) (8), and there is now ample evidence that protection against reinfection with the B.1.1.529/21K (Omicron) variant (9,10) is dramatically reduced compared with previous variants (**Table 1**).

Any descriptor of immunity based on patient history will encompass a population of individuals with vastly variable exposure to vaccines and viral variants with differing orders of immune challenge intensity. Unrecognised 'silent infections', especially in Omicron-positive subjects with underlying immunity, further complicate the assessment. Therefore derivation of potential immunity based on patient history requires assistance from a surrogate composite score to inform about protection and to aid decision making.

Correlates of protection or risk

In vaccinology, a correlate of protection (CoP) reflects a statistical non-causal relationship between an immune marker and protection after vaccination (11). Most accepted CoPs are based on antibody measurements (12) and vary depending on the clinical endpoint, for example protection from (symptomatic) infection or severe disease. In contrast, a correlate of risk (CoR) can be used as a measurement of an immunologic parameter that is correlated with a study endpoint (13) and can predict a clinical endpoint in a specified population with a defined future timeframe. Notably, antibody markers have been used as correlates of immune function in clinical trials of SARS-CoV-2 vaccine efficacy (14-19), and for identifying the risk of symptomatic infection by VOCs (20,21).

A CoR would likely comprise a measure of the immune component plus determinants that act to modify such a measure (a multi-component composite CoR). In general, the immune component of a composite CoR should be easily measured by widely available technologies that are amenable to automation, are scalable, cost-efficient, and have a rapid turn-around time. Given the relative complexity, cost and pre-analytic requirements for cellular immune response testing, the preferred candidate for the immune component of a CoR would be detection of humoral immune response(s) (i.e. antibody). This perspective evaluates the various elements that need to be accommodated in the development of an antibody-based composite CoR for reinfection with SARS-CoV-2 or severe COVID-19.

A composite CoR: A brief summary of extrinsic viral and intrinsic host elements that should be considered

Variation in exposure dose and transmission route

Viral load varies widely between infected individuals and over time (22), with viral emissions independent of symptom severity (23). Exposure to SARS-CoV-2 is tempered by the use of personal protective measures and, at the population level, adherence to public health measures that reduce exposure has been variable (24,25), making assessment of exposure dose complex.

Controlled human infections to directly study the impact of viral inoculum and disease severity are controversial (26), and only one human challenge trial of SARS-CoV-2 using a single low inoculum dose has been reported to date (27). However, the initial infective dose of SARS-CoV-2 is thought to be associated with disease severity (28-30), since relationships between dose and severity exist for many other viral infections (30). Evidence from SARS-CoV-2 animal models suggests that the route of transmission similarly affects disease severity (30,31).

Viral genetic variation

Risk reduction depends on the dominant variant in circulation. Continued evolution of SARS-CoV-2 can lead to significant changes in viral transmission and impact reinfection rates (32). Mechanistically, the receptor binding domain (RBD) within the viral spike (S) glycoprotein engages in initiation of infection via interaction with the angiotensin converting enzyme-2 (ACE2) receptor (33). The RBD is a target for many nAbs (33) and mutations are frequently located at the RBD–ACE2 interface (34). It is therefore not surprising that changes to the viral epitope can reduce antibody binding (34), helping to drive immune

escape from anti-RBD nAbs (35), decreasing previously generated protective immunity (36-38), and leading to variant-specific risks of severe illness (39,40).

Patient factors

Patient differences impact susceptibility to reinfection and disease severity. The immune response declines with increasing age (41,42), and age is the strongest predictor of SARS-CoV-2 infection–fatality ratio (43). Older individuals have been shown to exhibit reduced binding antibody titers and neutralization following vaccination (44-46). Pregnant women are also at high risk of severe outcomes (47). Similarly, immunocompromised or immunosuppressed individuals exhibit reduced immune responses to infection or an increased risk of hospitalization (48-51). Other co-morbidities are frequently observed in those with severe COVID-19 (52).

Vaccination status

COVID-19 vaccines include recombinant subunit, nucleic acid, viral vector and whole virus vaccines, amongst others, and some vaccines have been adapted for Omicron variants (53). The use of different vaccines, combinations, the number of boosters received, the occurrence of natural infection, and combinations thereof, trigger the immune system to varying degrees in depth, breadth or duration of response (21,54-66).

Following primary infection, severely ill patients exhibit higher binding and neutralizing antibody titers or activity compared with individuals with mild disease (67-72). Persistence of nAbs has also been associated with disease severity (73). In the event of reinfection, there is an implicit assumption that nAb titers ameliorate severe COVID-19 (74,75). In brief, in infection-naïve individuals, post-vaccination antibody titers (anti-S IgG and nAbs) correlate with higher vaccine efficacy (55), and post-vaccination anti-RBD IgG and nAbs levels associate with protection against infection and symptomatic disease even during the Omicron era (76) or inversely correlate with risk of death (anti-S IgG below 20^{th} percentile) (77). Generally, individuals with higher nAbs (levels or capacity) are considered increasingly protected from infection (78-80), symptomatic reinfection (80-82), severe disease (81), or death (83) compared with individuals with lower nAbs. There is evidence that neutralization capacity can be strain specific (84).

Summary

In summary, viral and host elements modify the risk of reinfection or development of severe COVID-19. Although not described above, other relevant factors include whether an individual previously received monoclonal antibodies (85) (but potentially not antiviral medication (86)), genetic predisposition (87-91), and socioeconomic, air pollution, co-infection, microbiota, and frailty factors (reviewed in detail (31)).

A composite CoR: Antibody dynamics, serology in practice and challenges, and expert recommendations

The antibody component of a composite CoR should be developed under defined conditions. To provide insight into these conditions, an understanding of antibody dynamics is required.

SARS-CoV-2 antibody dynamics

Natural infection with SARS-CoV-2 elicits a diversity of antibodies including those targeting S and nucleocapsid (N) antigens (59,92) and the development of anti-RBD IgG antibodies is associated with improved patient survival (93). A detailed systematic review of 66 studies investigated antibody responses (94). Collectively, the evidence supports the induction of IgM production in the acute phase of natural infection (peak

prevalence: 20 days) followed by IgA (peak prevalence: 23 days), IgG (peak prevalence: 25 days), and nAbs (peak prevalence: 31 days) after symptom onset (94).

Serum IgG has the longest half-life compared with the relatively transient IgA or IgM (95). A longitudinal analysis of 4558 individuals, measuring total anti-N antibodies, revealed that, whilst total antibodies begin to decline after 90–100 days, they may persist for over 500 days after natural infection (96). Specifically measuring nAb via plaque reduction neutralization test (PRNT) shows that infection yields a robust nAb response in most individuals (67). Some studies report that anti-S antibodies show greater persistence than anti-N antibodies (97,98).

Dramatic inductions of anti-S or anti-RBD IgG antibodies is indicative of vaccination (59,99,100). Primary vaccination by some vaccines, (but not all (101)), or boosters generates high nAb titers (100,102,103) or neutralizing responses (99). Notably, nAbs wane over time (21) with a half-life of 108 days (81) – although the level of decay may be assay or variant dependent (102) – and multiple clinical factors affect the duration of neutralization responses after primary vaccination (66).

Anti-SARS-CoV-2 antibody testing

Commercial high-throughput immunoassays

Numerous immunoassays for the detection of antibodies against SARS-CoV-2 are available, differing in the immunoglobulin class detected, target viral antigen, format, and output (qualitative, [semi]-quantitative) (reviewed in detail (104,105)).

Head-to-head comparisons from the pre-Omicron era reveal variable levels of performance between the assays (106-110), caused by numerous technical factors including assay methodology, format and antibodies used, timing of testing, and the targeted viral antigen. Comparison studies show that sensitivity for detecting prior infection by different serologic assays changes over time (111). Commercial assays developed early during the pandemic are based on ancestral/wild-type antigens. Subsequently, there is potential for differential performance in the Omicron-era: in particular, S- and RBD-specific immunoassays have shown significantly reduced performance (112-114), and decreased comparability of quantitative results (115).

Most common commercial immunoassays detect both binding and nAbs without differentiating between them, however certain assays measuring IgG or total antibodies correlate well with neutralizing capacity (14,78,116-122), acting as surrogates of neutralization. Cell-based virus neutralization tests can be used to measure neutralizing capability, but these are typically not readily available in clinical laboratories due to inherent test performance challenges associated with their methodology, time and cost (123).

Expert recommendations

Mature immune responses are dominated by IgG. Serologic assays that measure IgG or total antibodies (if skewed towards IgG) that correlate with neutralizing activity and focus on anti-RBD should be used for the serologic component of a composite CoR; anti-N antibodies are unlikely to be neutralizing as the N protein is located within the viral envelope (59).

Assays should be adapted for accurate measurement of the modified antigen, if applicable. However, frequent adaptation of assays is unlikely if several variants are circulating in parallel and due to regulatory requirements for assays. Therefore, studies are needed to determine assay applicability in the present conditions, especially since RBD mutations frequently occur and recombinant versions of RBD or S are commonly used in immunoassays (105). Accordingly, the upper and lower thresholds of any CoR may need modification.

External ring trials show poor comparability of assays from different manufacturers (124,125) and there are significant challenges with the current binding antibody units (BAU) standardization, due to multiple factors, including different assay methods, antibody class(es) detected and target antigen used. Of note, BAU reference materials were derived from UK convalescent individuals infected in 2020 (126) (pre-Omicron), and there are vastly different BAU standardized values (Kroidl et al 2023, submitted). Antibody measurements

should be harmonized across assays from different manufacturers, irrespective of the different epitopes utilized, to reduce variability. To support this, there is an urgent need for external quality assessment, production of robust traceable certified reference materials, standards for different variants, and improved documentation of the methods on laboratory reports. Age-specific normalization of reference intervals in defined groups, by means of z-log transformation and documentation in antibody passes, may further improve the comparability of assays. Stakeholders should agree on minimum performance-based criteria to develop the gold standard for CoR, allowing validation of secondary assays.

Finally, systemic cellular assays could provide a comprehensive profile of the immune response, especially in immunocompromised and susceptible individuals who are not able to mount a robust antibody response. Currently, they lack scientific evidence and their use in clinical practice still remains uncertain.

Sample matrices

Systemic anti-SARS-CoV-2 antibody testing can be performed on blood, plasma/serum, or dried blood spots (DBS) (105,127,128); Wieser et al 2023, submitted). An advantage of whole blood or DBS collection is the ease in obtaining the sample. Whilst many methodologies focus on systemic testing, infection with SARS-CoV-2 or vaccination against COVID-19 induces mucosal antibodies (129,130), thus secretions such as saliva offer another possibility. Antibody dynamics will differ depending on the material in question (131), and sample types are subject to specific idiosyncrasies, such as additional pre-processing, that need to be accounted for (132). Currently secretion-based testing is less suitable for a composite CoR as performance is variable (133).

Expert recommendations

A composite CoR will likely be sample matrix-specific. Our preference is for plasma/serum, as this sample matrix has the largest evidence base, shows the least variability, experiences less interference than whole blood, and is consistent with CoRs established for other infectious diseases. DBS would be also possible, but variability is high, and few laboratories have an established workflow.

Serologic testing formats

Formats include high-throughput automated enzyme immunoassay/ electrochemiluminescence immunoassay/enzyme-linked immunosorbent assay (certified and used in central laboratories and hospitals), point-of-care (POC) testing (used in emergencies and outpatients setting), and direct-to-consumer testing (at-home use with online services). POC testing is gaining in popularity, but methodological variation is higher (134) and any method that relies upon sampling from untrained individuals is less reliable for (semi)quantitative measurements (135).

Expert recommendations

We recommend automated assays that are approved by location-specific regulatory agencies and performed in certified and centralized laboratories. Home sampling/DBS would contribute to a reduction in clinician workload, particularly in high-density residential facilities, but methods are not yet sufficiently robust. At this time, there is no clear benefit in POC testing as urgent results are not critical.

Frequency of sampling and optimal time point

Considering antibody dynamics, several important questions arise: what is the optimal time point for measurement; would the timing differ depending on the vaccine schedule, and/or the presence of previous infection of a specified severity; should antibody levels be measured once or serially? Whilst single values can be plotted into modelled curves showing decrease rates over time, serial measurements could further refine the composite CoR. Only individuals with symptomatic disease or vaccination are known to stabilise the curve — infections that are sufficiently mild to lack detection will impact the composite CoR model.

Expert recommendations

As most individuals have experienced infection or vaccination, and titers are generally high and more stable than with single exposures, sampling should be performed annually or less. Serologic evaluation should be conducted more frequently in the elderly or immunocompromised than the general population (time interval to be defined), depending on any underlying disease and/or treatment.

Discussion

A composite CoR would be helpful particularly for high-risk groups, such as solid organ transplant recipients (136), and those in occupations with high risk of exposure to SARS-CoV-2. However, whether a composite CoR would operate at the individual or population level is yet uncertain.

For health policymakers, a composite CoR could be useful for: 1) predicting the durability of protection, supporting serosurveys to determine the protection levels of individuals and populations; 2) aiding decision-making with regard to monitoring vaccination efficacy and identifying individuals who would benefit from booster vaccinations; 3) evaluating the need for extra protection of vulnerable communities in the face of new variants with low cross protection and less efficacious vaccines; 4) licensing new vaccines; and 5) developing clear immunologic vaccine trial endpoints.

A previous systematic review by Perry and colleagues found mixed evidence for a serologic CoP, with the lack of standardization between laboratory methodology, differing assay targets and sampling time points, and the lack of information on the SARS-CoV-2 variant confounding interpretation (137). We have highlighted various parameters that should be controlled for in any measure of risk, some of which will be challenging to obtain (such as host genetics). Comparing different protection studies is also difficult as infectious pressure in the observation time period is often uncertain as, in reality, community data are incomplete and the number of oligosymptomatic infections is unclear. Of course, individual responses to infection and vaccination with regards to antibody production will make long-term assessment difficult, intrinsic risk will vary by age and protection will not be linear (122,138). All the variables previously described need to be thought of in the general context of laboratory diagnostics, paying attention to sensitivity, specificity, reliability, precision, dilution, linearity, robustness, stability, preanalytics, scalability (automation), cost-efficiency, In Vitro Diagnostic Regulation certification, and the use of qualified standard and control materials. Laboratory quality is essential for meaningful follow-up of quantitative antibody levels.

Whilst the development of a composite CoR is a sizeable task, steps can be taken to address this need. Studies need to adapt to the requirements of new variants, controlling for patient settings (vaccination types, earlier infections), and levels of disease severity. The emergence of VOCs means that a CoR will undoubtedly be variant-specific and the timing of infections and vaccination, how variants impact disease severity, antibody kinetics, and assay reactivity, must be respected. Frequently revisiting the data would be helpful as overall epidemiology changes; since almost all epidemiologic population-based studies have ended, background data is increasingly difficult to acquire, and this must be reversed. Whilst serologic testing has retreated from the political agenda and public interest, there is still an obligation to broaden the scientific knowledge base, and collect data to inform public health authorities, given that COVID-19 still causes a significant number of deaths and there is a considerable population of those with post-acute sequelae of SARS-CoV-2 infection (long COVID; (139)).

A composite CoR will differ depending on the clinical endpoint (12). Definitions of symptomatic or severe disease are often not consistent across studies (81). Clinical outcomes must be precisely defined: an evaluation of the primary endpoints of 19 clinical trials for severe COVID-19 revealed the complexity of this task, reporting 12 different primary endpoints (140). In addition, the ideal timeframe for predictive ability is yet to be determined.

Whilst we support the development of a composite CoR and serologic testing by high- quality controlled assays, viruses such as influenza have significant strain variation and similar disease severity, so the importance of a composite CoR for SARS-CoV-2 should be judged against other pathogens of interest. Assessment

of cost-effectiveness will likely inform upon the need for a composite CoR.

Conflict of Interest

Outside of the submitted work: **Stefan Holdenrieder** has received grants from Roche Diagnostics, Sysmex and Volition, consulting fees from Instand e.V, EQAS, Merck KG, Roche Diagnostics and Thermo Fisher Scientific, speaker's honoraria from BMS, Medica, Roche Diagnostics and Trillium, and has leadership roles in the International Society of Oncology and Biomarkers (board member and secretary), DGKL Competence Field Molecular Diagnostic (vice speaker) and Federal Medical Association, D5 Group (delegate of the DGKL); **Carlos Eduardo dos Santos Ferreira** has received speaker's honoraria from Abbott Diagnostics, Roche Diagnostics and Siemens Healthineers; **Jacques Izopet** has received grants from Roche Diagnostics; **Elitza Theel** has received consulting fees from EUROIMMUN US, Serimmune and Roche Diagnostics, speaker's honoraria from the American Society for Microbiology and EUROIMMUN US, and support for meetings from the American Society for Microbiology, the New York City Branch of the American Society of Microbiology and the Pan American Society for Clinical Virology; **Andreas Wieser** has received grants from numerous different public fundings, including the German Center for Infection Research, Fraunhofer Gesellschaft, and German Aif and Zim programs, royalties or licenses from Smart United GmbH, consulting fees from Roche Diagnostics and Roche Pharma, speaker's honoraria from BÄMI and Roche Diagnostics, support for meetings from BÄMI and Roche Diagnostics, participated in advisory boards for Roche Diagnostics, declares stock or stock options in Smart United GmbH and Munich Innovative Biosolutions UG (haftungsbeschrönkt), and has received reduced rates for materials and equipment from EUROIMMUN and Roche Diagnostics; **Stefan Holdenrieder** is a founder of CEBIO and SFZ BioCoDE.

Author Contributions

Stefan Holdenrieder and Andreas Wieser were involved in the Conceptualization, Writing - Original draft preparation, Writing - Reviewing and Editing of this manuscript. Carlos Eduardo dos Santos Ferreira, Jacques Izopet, and Elitza Theel were involved with Conceptualization, Writing - Reviewing and Editing of this manuscript. All authors approved the manuscript.

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References

1. Rahman MM, Masum MHU, Wajed S, Talukder A. A comprehensive review on COVID-19 vaccines: development, effectiveness, adverse effects, distribution and challenges. *Virusdisease* (2022) 33(1):1–22. Epub 2022/02/08. doi: 10.1007/s13337-022-00755-1.

2. Hale T, Angrist N, Goldszmidt R, Kira B, Petherick A, Phillips T, et al. A global panel database of pandemic policies (Oxford COVID-19 Government Response Tracker). *Nat Hum Behav* (2021) 5(4):529–38. Epub 2021/03/10. doi: 10.1038/s41562-021-01079-8.

3. Hale T, Petherick A, Anania J, Andretti B, Noam Angrist, Roy Barnes, et al. Variation in Government Responses to COVID-19. Version 14.1. Blavatnik School of Government Working Paper. 27 July 2022. www.bsg.ox.ac.uk/covidtracker (2022) [Accessed June 13, 2023].

4. Qi H, Liu B, Wang X, Zhang L. The humoral response and antibodies against SARS-CoV-2 infection. *Nature Immunology* (2022) 23(7):1008–20. doi: 10.1038/s41590-022-01248-5.

5. Liu M, Gan H, Liang Z, Liu L, Liu Q, Mai Y, et al. Review of therapeutic mechanisms and applications based on SARS-CoV-2 neutralizing antibodies. *Front Microbiol* (2023) 14:1122868. Epub 2023/04/04. doi: 10.3389/fmicb.2023.1122868.

6. Moss P. The T cell immune response against SARS-CoV-2. *Nature Immunology* (2022) 23(2):186–93. doi: 10.1038/s41590-021-01122-w.

7. Carabelli AM, Peacock TP, Thorne LG, Harvey WT, Hughes J, Peacock SJ, et al. SARS-CoV-2 variant biology: immune escape, transmission and fitness. *Nat Rev Microbiol* (2023) 21(3):162–77. Epub 2023/01/19. doi: 10.1038/s41579-022-00841-7.

8. World Health Organization. Updated working definitions and primary actions for SARS-CoV-2 variants. https://www.who.int/publications/m/item/updated-working-definitions-and-primary-actions-for–sars-cov-2-variants (2023) [Accessed April 13, 2023].

9. Viana R, Moyo S, Amoako DG, Tegally H, Scheepers C, Althaus CL, et al. Rapid epidemic expansion of the SARS-CoV-2 omicron variant in southern Africa. *Nature* (2022) 603(7902):679–86. Epub 2022/01/19. doi: 10.1038/s41586-022-04411-y.

10. World Health Organization. One year since the emergence of COVID-19 virus variant Omicron. https://www.who.int/news-room/feature-stories/detail/one-year-since-the-emergence-of-omicron#:˜:text=It%20was%2026%20November%202021,of%20the%20COVID%2D19%20pandemic. (2022) [Accessed April 17, 2023].

11. Plotkin SA, Gilbert PB. Nomenclature for immune correlates of protection after vaccination. *Clin Infect Dis* (2012) 54(11):1615–7. doi: 10.1093/cid/cis238.

12. Plotkin SA. Correlates of protection induced by vaccination. *Clin Vaccine Immunol* (2010) 17(7):1055–65. doi: 10.1128/CVI.00131-10.

13. Gilbert PB, Qin L, Self SG. Evaluating a surrogate endpoint at three levels, with application to vaccine development. *Stat Med* (2008) 27(23):4758–78. Epub 2007/11/06. doi: 10.1002/sim.3122.

14. Gilbert PB, Montefiori DC, McDermott AB, Fong Y, Benkeser D, Deng W, et al. Immune correlates analysis of the mRNA-1273 COVID-19 vaccine efficacy clinical trial. *Science* (2022) 375(6576):43–50. Epub 2021/11/24. doi: 10.1126/science.abm3425.

15. Fong Y, McDermott AB, Benkeser D, Roels S, Stieh DJ, Vandebosch A, et al. Immune correlates analysis of the ENSEMBLE single Ad26.COV2.S dose vaccine efficacy clinical trial. *Nat Microbiol* (2022) 7(12):1996–2010. Epub 2022/11/11. doi: 10.1038/s41564-022-01262-1.

16. Ramasamy MN, Minassian AM, Ewer KJ, Flaxman AL, Folegatti PM, Owens DR, et al. Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): a single-blind, randomised, controlled, phase 2/3 trial. *Lancet*(2021) 396(10267):1979–93. Epub 2020/11/23. doi: 10.1016/s0140-6736(20)32466-1.

17. Feng S, Phillips DJ, White T, Sayal H, Aley PK, Bibi S, et al. Correlates of protection against symptomatic and asymptomatic SARS-CoV-2 infection. *Nat Med* (2021) 27(11):2032–40. Epub 2021/10/01. doi:

10.1038/s41591-021-01540-1.

18. Li G, Cappuccini F, Marchevsky NG, Aley PK, Aley R, Anslow R, et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 (AZD1222) vaccine in children aged 6-17 years: a preliminary report of COV006, a phase 2 single-blind, randomised, controlled trial. *Lancet* (2022) 399(10342):2212–25. Epub 2022/06/13. doi: 10.1016/s0140-6736(22)00770-x.

19. Cristiano A, Nuccetelli M, Pieri M, Sarubbi S, Pelagalli M, Calugi G, et al. Serological anti-SARS-CoV-2 neutralizing antibodies association to live virus neutralizing test titers in COVID-19 paucisymptomatic/symptomatic patients and vaccinated subjects. *Int Immunopharmacol* (2021) 101(Pt B):108215. Epub 2021/10/15. doi: 10.1016/j.intimp.2021.108215.

20. Nilles EJ, Paulino CT, de St Aubin M, Duke W, Jarolim P, Sanchez IM, et al. Tracking immune correlates of protection for emerging SARS-CoV-2 variants. *Lancet Infect Dis* (2023) 23(2):153–4. Epub 2023/01/15. doi: 10.1016/s1473-3099(23)00001-4.

21. Cromer D, Steain M, Reynaldi A, Schlub TE, Wheatley AK, Juno JA, et al. Neutralising antibody titres as predictors of protection against SARS-CoV-2 variants and the impact of boosting: a meta-analysis.*Lancet Microbe* (2022) 3(1):e52–e61. Epub 2021/11/23. doi: 10.1016/s2666-5247(21)00267-6.

22. Jones TC, Biele G, Mühlemann B, Veith T, Schneider J, Beheim-Schwarzbach J, et al. Estimating infectiousness throughout SARS-CoV-2 infection course. *Science* (2021) 373(6551). Epub 2021/05/27. doi: 10.1126/science.abi5273.

23. Zhou J, Singanayagam A, Goonawardane N, Moshe M, Sweeney FP, Sukhova K, et al. Viral emissions into the air and environment after SARS-CoV-2 human challenge: a phase 1, open label, first-in-human study.*Lancet Microbe* (2023). Epub 2023/06/13. doi: 10.1016/s2666-5247(23)00101-5.

24. Kale D, Herbec A, Beard E, Gold N, Shahab L. Patterns and predictors of adherence to health-protective measures during COVID-19 pandemic in the UK: cross-sectional and longitudinal findings from the HEBECO study.*BMC Public Health* (2022) 22(1):2347. Epub 2022/12/15. doi: 10.1186/s12889-022-14509-7.

25. Hutchins HJ, Wolff B, Leeb R, Ko JY, Odom E, Willey J, et al. COVID-19 mitigation behaviors by age group - United States, April-June 2020. *MMWR Morb Mortal Wkly Rep* (2020) 69(43):1584–90. Epub 2020/10/30. doi: 10.15585/mmwr.mm6943e4.

26. Jamrozik E, Selgelid MJ. COVID-19 human challenge studies: ethical issues. *Lancet Infect Dis* (2020) 20(8):e198–e203. Epub 2020/06/02. doi: 10.1016/s1473-3099(20)30438-2.

27. Killingley B, Mann AJ, Kalinova M, Boyers A, Goonawardane N, Zhou J, et al. Safety, tolerability and viral kinetics during SARS-CoV-2 human challenge in young adults. *Nat Med* (2022) 28(5):1031–41. Epub 2022/04/02. doi: 10.1038/s41591-022-01780-9.

28. Khosroshahi HT, Mardomi A. The initial infectious dose of SARS-CoV-2 and the severity of the disease: possible impact on the incubation period. *Future Virol* (2021). doi: 10.2217/fvl-2020-0330.

29. Van Damme W, Dahake R, van de Pas R, Vanham G, Assefa Y. COVID-19: does the infectious inoculum dose-response relationship contribute to understanding heterogeneity in disease severity and transmission dynamics? *Med Hypotheses* (2021) 146:110431. Epub 2020/12/09. doi: 10.1016/j.mehy.2020.110431.

30. Spinelli MA, Glidden DV, Gennatas ED, Bielecki M, Beyrer C, Rutherford G, et al. Importance of non-pharmaceutical interventions in lowering the viral inoculum to reduce susceptibility to infection by SARS-CoV-2 and potentially disease severity. *Lancet Infect Dis*(2021) 21(9):e296–e301. Epub 2021/02/26. doi: 10.1016/s1473-3099(20)30982-8.

31. Zsichla L, Müller V. Risk factors of severe COVID-19: a review of host, viral and environmental factors. *Viruses* (2023) 15(1):175. Epub 2023/01/22. doi: 10.3390/v15010175.

32. Markov PV, Ghafari M, Beer M, Lythgoe K, Simmonds P, Stilianakis NI, et al. The evolution of SARS-CoV-2. *Nat Rev Microbiol* (2023) 21(6):361–79. Epub 2023/04/06. doi: 10.1038/s41579-023-00878-2.

33. Klasse PJ, Moore JP. Antibodies to SARS-CoV-2 and their potential for therapeutic passive immunization. *Elife* (2020) 9. Epub 2020/06/24. doi: 10.7554/eLife.57877.

34. Harvey WT, Carabelli AM, Jackson B, Gupta RK, Thomson EC, Harrison EM, et al. SARS-CoV-2 variants, spike mutations and immune escape.*Nat Rev Microbiol* (2021) 19(7):409–24. Epub 2021/06/03. doi: 10.1038/s41579-021-00573-0.

35. Souza PFN, Mesquita FP, Amaral JL, Landim PGC, Lima KRP, Costa MB, et al. The spike glycoprotein of SARS-CoV-2: a review of how mutations of spike glycoproteins have driven the emergence of variants with high transmissibility and immune escape. *Int J Biol Macromol* (2022) 208:105–25. Epub 2022/03/19. doi: 10.1016/j.ijbiomac.2022.03.058.

36. Liu C, Ginn HM, Dejnirattisai W, Supasa P, Wang B, Tuekprakhon A, et al. Reduced neutralization of SARS-CoV-2 B.1.617 by vaccine and convalescent serum. *Cell* (2021) 184(16):4220–36.e13. Epub 2021/07/10. doi: 10.1016/j.cell.2021.06.020.

37. Migueres M, Dimeglio C, Trémeaux P, Abravanel F, Raymond S, Lhomme S, et al. Influence of immune escape and nasopharyngeal virus load on the spread of SARS-CoV-2 Omicron variant. *J Infect* (2022) 84(4):e7–e9. Epub 2022/02/11. doi: 10.1016/j.jinf.2022.01.036.

38. Wang P, Nair MS, Liu L, Iketani S, Luo Y, Guo Y, et al. Antibody resistance of SARS-CoV-2 variants B.1.351 and B.1.1.7. *Nature*(2021) 593(7857):130–5. Epub 2021/03/09. doi: 10.1038/s41586-021-03398-2.

39. Kow CS, Ramachandram DS, Hasan SS. Risk of severe illness in patients infected with SARS-CoV-2 of Delta variant: a systematic review and meta-analysis. *Infect Dis (Lond)* (2022) 54(8):614–7. Epub 2022/04/08. doi: 10.1080/23744235.2022.2055787.

40. Kow CS, Ramachandram DS, Hasan SS. The risk of mortality and severe illness in patients infected with the omicron variant relative to delta variant of SARS-CoV-2: a systematic review and meta-analysis. *Ir J Med Sci* (2023):1–8. Epub 2023/02/09. doi: 10.1007/s11845-022-03266-6.

41. Ciabattini A, Nardini C, Santoro F, Garagnani P, Franceschi C, Medaglini D. Vaccination in the elderly: the challenge of immune changes with aging. *Semin Immunol* (2018) 40:83–94. Epub 2018/12/07. doi: 10.1016/j.smim.2018.10.010.

42. Nian Y, Minami K, Maenesono R, Iske J, Yang J, Azuma H, et al. Changes of T-cell immunity over a lifetime. *Transplantation*(2019) 103(11):2227–33. Epub 2019/05/21. doi: 10.1097/tp.0000000000002786.

43. COVID-19 Forecasting Team. Variation in the COVID-19 infection–fatality ratio by age, time, and geography during the pre-vaccine era: a systematic analysis. *Lancet* (2022) 399(10334):1469–88. doi: 10.1016/S0140-6736(21)02867-1.

44. Collier DA, Ferreira I, Kotagiri P, Datir RP, Lim EY, Touizer E, et al. Age-related immune response heterogeneity to SARS-CoV-2 vaccine BNT162b2. *Nature* (2021) 596(7872):417–22. Epub 2021/07/01. doi: 10.1038/s41586-021-03739-1.

45. Bichara CDA, Queiroz MAF, da Silva Graça Amoras E, Vaz GL, Vallinoto I, Bichara CNC, et al. Assessment of anti-SARS-CoV-2 antibodies post-Coronavac vaccination in the Amazon region of Brazil. *Vaccines* (2021) 9(10):1169. Epub 2021/10/27. doi: 10.3390/vaccines9101169.

46. Walsh EE, Frenck RW, Jr., Falsey AR, Kitchin N, Absalon J, Gurtman A, et al. Safety and immunogenicity of two RNA-based Covid-19 vaccine candidates. *N Engl J Med* (2020) 383(25):2439–50. Epub 2020/10/15. doi: 10.1056/NEJMoa2027906.

47. Allotey J, Stallings E, Bonet M, Yap M, Chatterjee S, Kew T, et al. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and

meta-analysis. *BMJ* (2020) 370:m3320. Epub 2020/09/03. doi: 10.1136/bmj.m3320.

48. Li J, Ayada I, Wang Y, den Hoed CM, Kamar N, Peppelenbosch MP, et al. Factors associated with COVID-19 vaccine response in transplant recipients: a systematic review and meta-analysis. *Transplantation* (2022) 106(10):2068–75. Epub 2022/06/29. doi: 10.1097/tp.0000000000004256.

49. Wankhede D, Grover S, Hofman P. Determinants of humoral immune response to SARS-CoV-2 vaccines in solid cancer patients: a systematic review and meta-analysis. *Vaccine* (2023). Epub 2023/02/16. doi: 10.1016/j.vaccine.2023.01.072.

50. Liu Y, Xiao Y, Wu S, Marley G, Ming F, Wang X, et al. People living with HIV easily lose their immune response to SARS-CoV-2: result from a cohort of COVID-19 cases in Wuhan, China. *BMC Infect Dis* (2021) 21(1):1029. Epub 2021/10/03. doi: 10.1186/s12879-021-06723-2.

51. Shen C, Risk M, Schiopu E, Hayek SS, Xie T, Holevinski L, et al. Efficacy of COVID-19 vaccines in patients taking immunosuppressants.*Ann Rheum Dis* (2022) 81(6):875–80. Epub 2022/02/25. doi: 10.1136/annrheumdis-2021-222045.

52. Kompaniyets L, Pennington AF, Goodman AB, Rosenblum HG, Belay B, Ko JY, et al. Underlying medical conditions and severe Illness among 540,667 adults hospitalized with COVID-19, March 2020-March 2021.*Prev Chronic Dis* (2021) 18:E66. Epub 2021/07/02. doi: 10.5888/pcd18.210123.

53. Yadav T, Kumar S, Mishra G, Saxena SK. Tracking the COVID-19 vaccines: the global landscape. *Hum Vaccin Immunother* (2023) 19(1):2191577. Epub 2023/03/31. doi: 10.1080/21645515.2023.2191577.

54. Lim SY, Kim JY, Jung J, Yun SC, Kim SH. Waning of humoral immunity depending on the types of COVID-19 vaccine. *Infect Dis (Lond)*(2023) 55(3):216–20. Epub 2023/01/11. doi: 10.1080/23744235.2023.2165707.

55. Earle KA, Ambrosino DM, Fiore-Gartland A, Goldblatt D, Gilbert PB, Siber GR, et al. Evidence for antibody as a protective correlate for COVID-19 vaccines. *Vaccine* (2021) 39(32):4423–8. Epub 2021/07/03. doi: 10.1016/j.vaccine.2021.05.063.

56. Nham E, Ko JH, Song KH, Choi JY, Kim ES, Kim HJ, et al. Kinetics of vaccine-induced neutralizing antibody titers and estimated protective immunity against wild-type SARS-CoV-2 and the Delta variant: a prospective nationwide cohort study comparing three COVID-19 vaccination protocols in South Korea. *Front Immunol* (2022) 13:968105. Epub 2022/10/11. doi: 10.3389/fimmu.2022.968105.

57. Lafon E, Jäger M, Bauer A, Reindl M, Bellmann-Weiler R, Wilflingseder D, et al. Comparative analyses of IgG/IgA neutralizing effects induced by three COVID-19 vaccines against variants of concern.*J Allergy Clin Immunol* (2022) 149(4):1242–52.e12. Epub 2022/01/31. doi: 10.1016/j.jaci.2022.01.013.

58. Greaney AJ, Loes AN, Gentles LE, Crawford KHD, Starr TN, Malone KD, et al. Antibodies elicited by mRNA-1273 vaccination bind more broadly to the receptor binding domain than do those from SARS-CoV-2 infection.*Sci Transl Med* (2021) 13(600). Epub 2021/06/10. doi: 10.1126/scitranslmed.abi9915.

59. Meyers J, Windau A, Schmotzer C, Saade E, Noguez J, Stempak L, et al. SARS-CoV-2 antibody profile of naturally infected and vaccinated individuals detected using qualitative, semi-quantitative and multiplex immunoassays. *Diagn Microbiol Infect Dis* (2022) 104(4):115803. Epub 2022/09/27. doi: 10.1016/j.diagmicrobio.2022.115803.

60. Townsend JP, Hassler HB, Sah P, Galvani AP, Dornburg A. The durability of natural infection and vaccine-induced immunity against future infection by SARS-CoV-2. *Proc Natl Acad Sci U S A* (2022) 119(31):e2204336119. Epub 2022/07/21. doi: 10.1073/pnas.2204336119.

61. Yu Y, Esposito D, Kang Z, Lu J, Remaley AT, De Giorgi V, et al. mRNA vaccine-induced antibodies more effective than natural immunity in neutralizing SARS-CoV-2 and its high affinity variants. *Sci Rep*(2022) 12(1):2628. Epub 2022/02/18. doi: 10.1038/s41598-022-06629-2.

62. Vietri MT, D'Elia G, Caliendo G, Passariello L, Albanese L, Molinari AM, et al. Antibody levels after BNT162b2 vaccine booster and SARS-CoV-2 Omicron infection. *Vaccine* (2022) 40(39):5726–31. Epub 2022/08/31. doi: 10.1016/j.vaccine.2022.08.045.

63. Munro APS, Janani L, Cornelius V, Aley PK, Babbage G, Baxter D, et al. Safety and immunogenicity of seven COVID-19 vaccines as a third dose (booster) following two doses of ChAdOx1 nCov-19 or BNT162b2 in the UK (COV-BOOST): a blinded, multicentre, randomised, controlled, phase 2 trial. *Lancet* (2021) 398(10318):2258–76. Epub 2021/12/06. doi: 10.1016/s0140-6736(21)02717-3.

64. Andrews N, Tessier E, Stowe J, Gower C, Kirsebom F, Simmons R, et al. Duration of protection against mild and severe disease by Covid-19 vaccines. *N Engl J Med* (2022) 386(4):340–50. Epub 2022/01/13. doi: 10.1056/NEJMoa2115481.

65. Cerqueira-Silva T, Andrews JR, Boaventura VS, Ranzani OT, de Araújo Oliveira V, Paixão ES, et al. Effectiveness of CoronaVac, ChAdOx1 nCoV-19, BNT162b2, and Ad26.COV2.S among individuals with previous SARS-CoV-2 infection in Brazil: a test-negative, case-control study.*Lancet Infect Dis* (2022) 22(6):791–801. Epub 2022/04/04. doi: 10.1016/s1473-3099(22)00140-2.

66. Zhao M, Slotkin R, Sheth AH, Pischel L, Kyriakides TC, Emu B, et al. Serum neutralizing antibody titers 12 months after coronavirus disease 2019 messenger RNA vaccination: correlation to clinical variables in an adult, US population. *Clin Infect Dis* (2023) 76(3):e391–e9. Epub 2022/06/01. doi: 10.1093/cid/ciac416.

67. Lau EHY, Tsang OTY, Hui DSC, Kwan MYW, Chan WH, Chiu SS, et al. Neutralizing antibody titres in SARS-CoV-2 infections. *Nat Commun*(2021) 12(1):63. Epub 2021/01/06. doi: 10.1038/s41467-020-20247-4.

68. Vanshylla K, Di Cristanziano V, Kleipass F, Dewald F, Schommers P, Gieselmann L, et al. Kinetics and correlates of the neutralizing antibody response to SARS-CoV-2 infection in humans. *Cell Host Microbe* (2021) 29(6):917–29.e4. Epub 2021/05/14. doi: 10.1016/j.chom.2021.04.015.

69. Chen X, Pan Z, Yue S, Yu F, Zhang J, Yang Y, et al. Disease severity dictates SARS-CoV-2-specific neutralizing antibody responses in COVID-19. *Signal Transduct Target Ther* (2020) 5(1):180. Epub 2020/09/04. doi: 10.1038/s41392-020-00301-9.

70. Maciola AK, La Raja M, Pacenti M, Salata C, De Silvestro G, Rosato A, et al. Neutralizing antibody responses to SARS-CoV-2 in recovered COVID-19 patients are variable and correlate with disease severity and receptor-binding domain recognition. *Front Immunol* (2022) 13:830710. Epub 2022/02/18. doi: 10.3389/fimmu.2022.830710.

71. Hansen CB, Jarlhelt I, Pérez-Alós L, Hummelshøj Landsy L, Loftager M, Rosbjerg A, et al. SARS-CoV-2 antibody responses are correlated to disease severity in COVID-19 convalescent individuals. *J Immunol*(2021) 206(1):109–17. Epub 2020/11/20. doi: 10.4049/jimmunol.2000898.

72. Wang P, Liu L, Nair MS, Yin MT, Luo Y, Wang Q, et al. SARS-CoV-2 neutralizing antibody responses are more robust in patients with severe disease. *Emerg Microbes Infect* (2020) 9(1):2091–3. Epub 2020/09/16. doi: 10.1080/22221751.2020.1823890.

73. Chia WN, Zhu F, Ong SWX, Young BE, Fong SW, Le Bert N, et al. Dynamics of SARS-CoV-2 neutralising antibody responses and duration of immunity: a longitudinal study. *Lancet Microbe* (2021) 2(6):e240–e9. Epub 2021/03/30. doi: 10.1016/s2666-5247(21)00025-2.

74. U.S Food and Drug Administration. EUA for convalescent plasma. https://www.fda.gov/media/141477/download (2021) [Accessed June 23, 2023].

75. U.S Food and Drug Administration. EUA for casirivimab and imdevimab. https://www.fda.gov/media/143891/download (2020) [Accessed June 23, 2023].

76. Gilboa M, Gonen T, Barda N, Cohn S, Indenbaum V, Weiss-Ottolenghi Y, et al. Factors associated with protection from SARS-CoV-2 omicron variant infection and disease among vaccinated health care

workers in Israel. *JAMA Netw Open* (2023) 6(5):e2314757. Epub 2023/05/23. doi: 10.1001/jamanetworkopen.2023.14757.

77. Vikström L, Fjällström P, Gwon YD, Sheward DJ, Wigren-Byström J, Evander M, et al. Vaccine-induced correlate of protection against fatal COVID-19 in older and frail adults during waves of neutralization-resistant variants of concern: an observational study.*Lancet Reg Health Eur* (2023) 30:100646. Epub 2023/06/26. doi: 10.1016/j.lanepe.2023.100646.

78. Dimeglio C, Herin F, Martin-Blondel G, Miedougé M, Izopet J. Antibody titers and protection against a SARS-CoV-2 infection. *J Infect* (2022) 84(2):248–88. Epub 2021/09/25. doi: 10.1016/j.jinf.2021.09.013.

79. Bergwerk M, Gonen T, Lustig Y, Amit S, Lipsitch M, Cohen C, et al. Covid-19 breakthrough infections in vaccinated health care workers.*N Engl J Med* (2021) 385(16):1474–84. Epub 2021/07/29. doi: 10.1056/NEJMoa2109072.

80. Lumley SF, O'Donnell D, Stoesser NE, Matthews PC, Howarth A, Hatch SB, et al. Antibody status and incidence of SARS-CoV-2 infection in health care workers. *N Engl J Med* (2021) 384(6):533–40. Epub 2020/12/29. doi: 10.1056/NEJMoa2034545.

81. Khoury DS, Cromer D, Reynaldi A, Schlub TE, Wheatley AK, Juno JA, et al. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. *Nat Med* (2021) 27(7):1205–11. Epub 2021/05/19. doi: 10.1038/s41591-021-01377-8.

82. Gillot C, Bayart JL, Closset M, Cabo J, Maloteau V, Dogné JM, et al. Peri-infection titers of neutralizing and binding antibodies as a predictor of COVID-19 breakthrough infections in vaccinated healthcare professionals: importance of the timing. *Clin Chem Lab Med* (2023) 61(9):1670–5. Epub 2023/04/01. doi: 10.1515/cclm-2023-0134.

83. Dispinseri S, Secchi M, Pirillo MF, Tolazzi M, Borghi M, Brigatti C, et al. Neutralizing antibody responses to SARS-CoV-2 in symptomatic COVID-19 is persistent and critical for survival. *Nat Commun*(2021) 12(1):2670. Epub 2021/05/13. doi: 10.1038/s41467-021-22958-8.

84. Dimeglio C, Herin F, Da-Silva I, Gernigon C, Porcheron M, Chapuy-Regaud S, et al. Decreased efficiency of neutralizing antibodies from previously infected or vaccinated individuals against the B.1.617.2 (delta) SARS-CoV-2 variant. *Microbiol Spectr* (2022) 10(4):e0270621. Epub 2022/07/23. doi: 10.1128/spectrum.02706-21.

85. Kim PS, Dimcheff DE, Siler A, Schildhouse RJ, Chensue SW. Effect of monoclonal antibody therapy on the endogenous SARS-CoV-2 antibody response. *Clin Immunol* (2022) 236:108959. Epub 2022/02/27. doi: 10.1016/j.clim.2022.108959.

86. Epling BP, Rocco JM, Boswell KL, Laidlaw E, Galindo F, Kellogg A, et al. Clinical, virologic, and immunologic evaluation of symptomatic coronavirus disease 2019 rebound following nirmatrelvir/ritonavir treatment. *Clin Infect Dis* (2023) 76(4):573–81. Epub 2022/10/07. doi: 10.1093/cid/ciac663.

87. Shelton JF, Shastri AJ, Ye C, Weldon CH, Filshtein-Sonmez T, Coker D, et al. Trans-ancestry analysis reveals genetic and nongenetic associations with COVID-19 susceptibility and severity. *Nat Genet*(2021) 53(6):801–8. Epub 2021/04/24. doi: 10.1038/s41588-021-00854-7.

88. Pairo-Castineira E, Clohisey S, Klaric L, Bretherick AD, Rawlik K, Pasko D, et al. Genetic mechanisms of critical illness in COVID-19.*Nature* (2021) 591(7848):92–8. Epub 2020/12/12. doi: 10.1038/s41586-020-03065-y.

89. Matuozzo D, Talouarn E, Marchal A, Zhang P, Manry J, Seeleuthner Y, et al. Rare predicted loss-of-function variants of type I IFN immunity genes are associated with life-threatening COVID-19. *Genome Med*(2023) 15(1):22. Epub 2023/04/06. doi: 10.1186/s13073-023-01173-8.

90. Kousathanas A, Pairo-Castineira E, Rawlik K, Stuckey A, Odhams CA, Walker S, et al. Whole-genome sequencing reveals host factors underlying critical COVID-19. *Nature* (2022) 607(7917):97–103. Epub 2022/03/08. doi: 10.1038/s41586-022-04576-6.

91. COVID-19 Host Genetics Initiative. Mapping the human genetic architecture of COVID-19. *Nature* (2021) 600(7889):472–7. Epub 2021/07/08. doi: 10.1038/s41586-021-03767-x.

92. Azak E, Karadenizli A, Uzuner H, Karakaya N, Canturk NZ, Hulagu S. Comparison of an inactivated Covid19 vaccine-induced antibody response with concurrent natural Covid19 infection. *Int J Infect Dis*(2021) 113:58–64. Epub 2021/10/02. doi: 10.1016/j.ijid.2021.09.060.

93. Secchi M, Bazzigaluppi E, Brigatti C, Marzinotto I, Tresoldi C, Rovere-Querini P, et al. COVID-19 survival associates with the immunoglobulin response to the SARS-CoV-2 spike receptor binding domain.*J Clin Invest* (2020) 130(12):6366–78. Epub 2020/09/30. doi: 10.1172/jci142804.

94. Arkhipova-Jenkins I, Helfand M, Armstrong C, Gean E, Anderson J, Paynter RA, et al. Antibody response after SARS-CoV-2 infection and implications for immunity: a rapid living review. *Ann Intern Med*(2021) 174(6):811–21. Epub 2021/03/16. doi: 10.7326/m20-7547.

95. Sterlin D, Mathian A, Miyara M, Mohr A, Anna F, Claër L, et al. IgA dominates the early neutralizing antibody response to SARS-CoV-2.*Sci Transl Med* (2021) 13(577). Epub 2020/12/09. doi: 10.1126/scitranslmed.abd2223.

96. Swartz MD, DeSantis SM, Yaseen A, Brito FA, Valerio-Shewmaker MA, Messiah SE, et al. Antibody duration after infection from SARS-CoV-2 in the Texas coronavirus antibody rresponse survey. *J Infect Dis*(2023) 227(2):193–201. Epub 2022/05/07. doi: 10.1093/infdis/jiac167.

97. Abraha I, Eusebi P, Germani A, Pasquarelli E, Pascolini S, Antonietti R, et al. Temporal trends and differences of SARS-CoV-2-specific antibody responses in symptomatic and asymptomatic subjects: a longitudinal study from Umbria in Italy. *BMJ Open*(2022) 12(7):e056370. Epub 2022/07/20. doi: 10.1136/bmjopen-2021-056370.

98. Ripperger TJ, Uhrlaub JL, Watanabe M, Wong R, Castaneda Y, Pizzato HA, et al. Orthogonal SARS-CoV-2 serological assays enable surveillance of low-prevalence communities and reveal durable humoral immunity.*Immunity* (2020) 53(5):925–33.e4. Epub 2020/11/02. doi: 10.1016/j.immuni.2020.10.004.

99. Hvidt AK, Baerends EAM, Søgaard OS, Stærke NB, Raben D, Reekie J, et al. Comparison of vaccine-induced antibody neutralization against SARS-CoV-2 variants of concern following primary and booster doses of COVID-19 vaccines. *Front Med (Lausanne)* (2022) 9:994160. Epub 2022/10/21. doi: 10.3389/fmed.2022.994160.

100. Rosseto-Welter EA, Rodrigues SS, de Figueiredo AB, França CN, Oliveira DBL, Bachi ALL, et al. Cellular and humoral immune responses to vaccination for COVID-19 are negatively impacted by senescent T cells: a case report. *Vaccines* (2023) 11(4):840. Epub 2023/04/28. doi: 10.3390/vaccines11040840.

101. Omran EA, Habashy RE, Ezz Elarab LA, Hashish MH, El-Barrawy MA, Abdelwahab IA, et al. Anti-spike and neutralizing antibodies after two doses of COVID-19 sinopharm/BIBP vaccine. *Vaccines* (2022) 10(8):1340. Epub 2022/08/27. doi: 10.3390/vaccines10081340.

102. Lyke KE, Atmar RL, Islas CD, Posavad CM, Szydlo D, Paul Chourdhury R, et al. Rapid decline in vaccine-boosted neutralizing antibodies against SARS-CoV-2 omicron variant. *Cell Rep Med* (2022) 3(7):100679. Epub 2022/07/08. doi: 10.1016/j.xcrm.2022.100679.

103. Furukawa K, Tjan LH, Kurahashi Y, Sutandhio S, Nishimura M, Arii J, et al. Assessment of neutralizing antibody response against SARS-CoV-2 variants after 2 to 3 doses of the BNT162b2 mRNA COVID-19 vaccine.*JAMA Netw Open* (2022) 5(5):e2210780. Epub 2022/05/10. doi: 10.1001/jamanetworkopen.2022.10780.

104. Fox T, Geppert J, Dinnes J, Scandrett K, Bigio J, Sulis G, et al. Antibody tests for identification of current and past infection with SARS-CoV-2. *Cochrane Database Syst Rev* (2022) 11(11):Cd013652. Epub 2022/11/18. doi: 10.1002/14651858.CD013652.pub2.

105. Theel ES. Performance characteristics of high-throughput serologic assays for severe acute respiratory syndrome coronavirus 2 with Food and Drug Administration Emergency Use authorization: a review. *Clin Lab Med* (2022) 42(1):15–29. Epub 2022/02/15. doi: 10.1016/j.cll.2021.10.006.

106. Olbrich L, Castelletti N, Schälte Y, Garí M, Pütz P, Bakuli A, et al. Head-to-head evaluation of seven different seroassays including direct viral neutralisation in a representative cohort for SARS-CoV-2.*J Gen Virol* (2021) 102(10):001653. Epub 2021/10/09. doi: 10.1099/jgv.0.001653.

107. The National SARS-CoV-2 Serology Assay Evaluation Group. Performance characteristics of five immunoassays for SARS-CoV-2: a head-to-head benchmark comparison. *Lancet Infect Dis* (2020) 20(12):1390–400. Epub 2020/09/27. doi: 10.1016/s1473-3099(20)30634-4.

108. Harritshøj LH, Gybel-Brask M, Afzal S, Kamstrup PR, Jørgensen CS, Thomsen MK, et al. Comparison of 16 serological SARS-CoV-2 immunoassays in 16 clinical laboratories. *J Clin Microbiol* (2021) 59(5). Epub 2021/02/13. doi: 10.1128/jcm.02596-20.

109. Chiereghin A, Zagari RM, Galli S, Moroni A, Gabrielli L, Venturoli S, et al. Recent advances in the evaluation of serological assays for the diagnosis of SARS-CoV-2 infection and COVID-19. *Front Public Health* (2020) 8:620222. Epub 2021/03/09. doi: 10.3389/fpubh.2020.620222.

110. Riester E, Findeisen P, Hegel JK, Kabesch M, Ambrosch A, Rank CM, et al. Performance evaluation of the Roche Elecsys Anti-SARS-CoV-2 S immunoassay. *J Virol Methods* (2021) 297:114271. Epub 2021/08/31. doi: 10.1016/j.jviromet.2021.114271.

111. Muecksch F, Wise H, Batchelor B, Squires M, Semple E, Richardson C, et al. Longitudinal serological analysis and neutralizing antibody levels in coronavirus disease 2019 convalescent patients. *J Infect Dis* (2021) 223(3):389–98. Epub 2020/11/04. doi: 10.1093/infdis/jiaa659.

112. Migueres M, Chapuy-Regaud S, Miédougé M, Jamme T, Lougarre C, Da Silva I, et al. Current immunoassays and detection of antibodies elicited by Omicron SARS-CoV-2 infection. *J Med Virol* (2023) 95(1):e28200. Epub 2022/10/09. doi: 10.1002/jmv.28200.

113. Springer DN, Perkmann T, Jani CM, Mucher P, Prüger K, Marculescu R, et al. Reduced sensitivity of commercial spike-specific antibody assays after primary infection with the SARS-CoV-2 Omicron variant.*Microbiol Spectr* (2022) 10(5):e0212922. Epub 2022/08/26. doi: 10.1128/spectrum.02129-22.

114. Habermann E, Frommert LM, Ghannam K, Nguyen My L, Gieselmann L, Tober-Lau P, et al. Performance of commercial SARS-CoV-2 wild-type and Omicron BA.1 antibody assays compared with pseudovirus neutralization tests. *J Clin Virol* (2023) 165:105518. Epub 2023/06/25. doi: 10.1016/j.jcv.2023.105518.

115. Rössler A, Knabl L, Raschbichler LM, Peer E, von Laer D, Borena W, et al. Reduced sensitivity of antibody tests after omicron infection.*Lancet Microbe* (2023) 4(1):e10–e1. Epub 2022/09/23. doi: 10.1016/s2666-5247(22)00222-1.

116. Montesinos I, Dahma H, Wolff F, Dauby N, Delaunoy S, Wuyts M, et al. Neutralizing antibody responses following natural SARS-CoV-2 infection: dynamics and correlation with commercial serologic tests.*J Clin Virol* (2021) 144:104988. Epub 2021/10/05. doi: 10.1016/j.jcv.2021.104988.

117. Theel ES, Johnson PW, Kunze KL, Wu L, Gorsh AP, Granger D, et al. SARS-CoV-2 serologic assays dependent on dual-antigen binding demonstrate diverging kinetics relative to other antibody detection methods. *J Clin Microbiol* (2021) 59(9):e0123121. Epub 2021/06/25. doi: 10.1128/jcm.01231-21.

118. Chapuy-Regaud S, Miédougé M, Abravanel F, Da Silva I, Porcheron M, Fillaux J, et al. Evaluation of three quantitative anti-SARS-CoV-2 antibody immunoassays. *Microbiol Spectr* (2021) 9(3):e0137621. Epub

2021/12/24. doi: 10.1128/spectrum.01376-21.

119. Lustig Y, Sapir E, Regev-Yochay G, Cohen C, Fluss R, Olmer L, et al. BNT162b2 COVID-19 vaccine and correlates of humoral immune responses and dynamics: a prospective, single-centre, longitudinal cohort study in health-care workers. *Lancet Respir Med* (2021) 9(9):999–1009. Epub 2021/07/06. doi: 10.1016/s2213-2600(21)00220-4.

120. Rubio-Acero R, Castelletti N, Fingerle V, Olbrich L, Bakuli A, Wölfel R, et al. In search of the SARS-CoV-2 protection correlate: head-to-head comparison of two quantitative S1 assays in pre-characterized oligo-/asymptomatic patients. *Infect Dis Ther*(2021) 10(3):1505–18. Epub 2021/06/18. doi: 10.1007/s40121-021-00475-x.

121. Jochum S, Kirste I, Hortsch S, Grunert VP, Legault H, Eichenlaub U, et al. Clinical utility of Elecsys anti-SARS-CoV-2 S assay in COVID-19 vaccination: an exploratory analysis of the mRNA-1273 Phase 1 trial.*Front Immunol* (2021) 12:798117. Epub 2022/02/08. doi: 10.3389/fimmu.2021.798117.

122. Regev-Yochay G, Lustig Y, Joseph G, Gilboa M, Barda N, Gens I, et al. Correlates of protection against COVID-19 infection and intensity of symptomatic disease in vaccinated individuals exposed to SARS-CoV-2 in households in Israel (ICoFS): a prospective cohort study. *Lancet Microbe* (2023) 4(5):e309–e18. Epub 2023/03/25. doi: 10.1016/s2666-5247(23)00012-5.

123. Lu Y, Wang J, Li Q, Hu H, Lu J, Zeliang C. Advances in neutralization assays for SARS-CoV-2. *Scand J Immunol* (2021) 94:e13088.

124. Ast V, Costina V, Eichner R, Bode A, Aida S, Gerhards C, et al. Assessing the quality of serological testing in the COVID-19 pandemic: results of a European External Quality Assessment (EQA) scheme for anti-SARS-CoV-2 antibody detection. *J Clin Microbiol* (2021) 59(9):e0055921. Epub 2021/07/01. doi: 10.1128/JCM.00559-21.

125. Perkmann T, Mucher P, Osze D, Muller A, Perkmann-Nagele N, Koller T, et al. Comparison of five Anti-SARS-CoV-2 antibody assays across three doses of BNT162b2 reveals insufficient standardization of SARS-CoV-2 serology. *J Clin Virol* (2023) 158:105345. Epub 2022/12/04. doi: 10.1016/j.jcv.2022.105345.

126. World Health Organization. Establishment of the WHO International Standard and Reference Panel for anti-SARS-CoV-2 antibody. 2020, WHO Expert Committee on Biological Standardization (WHO/BS/2020.2403). https://www.who.int/publications/m/item/WHO-BS-2020.2403 (2020) [Accessed June 23, 2023].

127. Beyerl J, Rubio-Acero R, Castelletti N, Paunovic I, Kroidl I, Khan ZN, et al. A dried blood spot protocol for high throughput analysis of SARS-CoV-2 serology based on the Roche Elecsys anti-N assay.*EBioMedicine* (2021) 70:103502. Epub 2021/08/02. doi: 10.1016/j.ebiom.2021.103502.

128. Decru B, Van Elslande J, Weemaes M, Houben E, Empsen I, André E, et al. Comparison of the diagnostic performance with whole blood and plasma of four rapid antibody tests for SARS-CoV-2. *Clin Chem Lab Med*(2020) 58(10):e197–e9. Epub 2020/07/07. doi: 10.1515/cclm-2020-0817.

129. Fröberg J, Diavatopoulos DA. Mucosal immunity to severe acute respiratory syndrome coronavirus 2 infection. *Curr Opin Infect Dis* (2021) 34(3):181–6. Epub 2021/04/27. doi: 10.1097/qco.0000000000000724.

130. Guerrieri M, Francavilla B, Fiorelli D, Nuccetelli M, Passali FM, Coppeta L, et al. Nasal and salivary mucosal humoral immune response elicited by mRNA BNT162b2 COVID-19 vaccine compared to SARS-CoV-2 natural infection. *Vaccines* (2021) 9(12). Epub 2021/12/29. doi: 10.3390/vaccines9121499.

131. Cervia C, Nilsson J, Zurbuchen Y, Valaperti A, Schreiner J, Wolfensberger A, et al. Systemic and mucosal antibody responses specific to SARS-CoV-2 during mild versus severe COVID-19. *J Allergy Clin Immunol* (2021) 147(2):545–57.e9. Epub 2020/11/23. doi: 10.1016/j.jaci.2020.10.040.

132. Russell MW, Mestecky J. Mucosal immunity: the missing link in comprehending SARS-CoV-2 infection and transmission. *Front Immunol* (2022) 13:957107. Epub 2022/09/06. doi: 10.3389/fimmu.2022.957107.

133. Heaney CD, Pisanic N, Randad PR, Kruczynski K, Howard T, Zhu X, et al. Comparative performance of multiplex salivary and commercially available serologic assays to detect SARS-CoV-2 IgG and neutralization titers. *J Clin Virol* (2021) 145:104997. doi: 10.1016/j.jcv.2021.104997.

134. Conklin SE, Martin K, Manabe YC, Schmidt HA, Miller J, Keruly M, et al. Evaluation of serological SARS-CoV-2 lateral flow assays for rapid point-of-care testing. *J Clin Microbiol* (2021) 59(2):e02020-20. Epub 2020/11/20. doi: 10.1128/jcm.02020-20.

135. Sims MD, Podolsky RH, Childers KL, Higgins B, Trueman J, Homayouni R, et al. Dried blood spots are a valid alternative to venipuncture for COVID-19 antibody testing. *J Immunol Methods* (2023) 513:113420. Epub 2023/01/04. doi: 10.1016/j.jim.2022.113420.

136. Kaufman HW, Meyer WA, Clarke NJ, Radcliff J, Rank CM, Freeman J, et al. Assessing vulnerability to COVID-19 in high-risk populations: the role of SARS-CoV-2 spike-targeted serology. *Popul Health Manag*(2023) 26(1):29–36. Epub 2023/02/18. doi: 10.1089/pop.2022.0241.

137. Perry J, Osman S, Wright J, Richard-Greenblatt M, Buchan SA, Sadarangani M, et al. Does a humoral correlate of protection exist for SARS-CoV-2? A systematic review. *PLoS One* (2022) 17(4):e0266852. Epub 2022/04/09. doi: 10.1371/journal.pone.0266852.

138. Haveri A, Solastie A, Ekström N, Österlund P, Nohynek H, Nieminen T, et al. Neutralizing antibodies to SARS-CoV-2 Omicron variant after third mRNA vaccination in health care workers and elderly subjects.*Eur J Immunol* (2022) 52(5):816–24. Epub 2022/03/22. doi: 10.1002/eji.202149785.

139. O'Mahoney LL, Routen A, Gillies C, Ekezie W, Welford A, Zhang A, et al. The prevalence and long-term health effects of Long Covid among hospitalised and non-hospitalised populations: A systematic review and meta-analysis. *EClinicalMedicine* (2023) 55:101762. Epub 2022/12/08. doi: 10.1016/j.eclinm.2022.101762.

140. Desai A, Kulkarni A, Rajkumar SV, Gyawali B. Clinical trial end points in severe COVID-19. *Mayo Clin Proc* (2020) 95(8):1578–80. Epub 2020/08/06. doi: 10.1016/j.mayocp.2020.05.025.

141. Hansen CH, Michlmayr D, Gubbels SM, Mølbak K, Ethelberg S. Assessment of protection against reinfection with SARS-CoV-2 among 4 million PCR-tested individuals in Denmark in 2020: a population-level observational study. *Lancet* (2021) 397(10280):1204–12. Epub 2021/03/21. doi: 10.1016/s0140-6736(21)00575-4.

142. Abu-Raddad LJ, Chemaitelly H, Coyle P, Malek JA, Ahmed AA, Mohamoud YA, et al. SARS-CoV-2 antibody-positivity protects against reinfection for at least seven months with 95% efficacy. *EClinicalMedicine*(2021) 35:100861. Epub 2021/05/04. doi: 10.1016/j.eclinm.2021.100861.

143. Hall VJ, Foulkes S, Charlett A, Atti A, Monk EJM, Simmons R, et al. SARS-CoV-2 infection rates of antibody-positive compared with antibody-negative health-care workers in England: a large, multicentre, prospective cohort study (SIREN). *Lancet* (2021) 397(10283):1459–69. Epub 2021/04/13. doi: 10.1016/s0140-6736(21)00675-9.

144. Lumley SF, Rodger G, Constantinides B, Sanderson N, Chau KK, Street TL, et al. An observational cohort study on the incidence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and B.1.1.7 variant infection in healthcare workers by antibody and vaccination status. *Clin Infect Dis* (2022) 74(7):1208–19. Epub 2021/07/04. doi: 10.1093/cid/ciab608.

145. Abu-Raddad LJ, Chemaitelly H, Ayoub HH, Coyle P, Malek JA, Ahmed AA, et al. Introduction and expansion of the SARS-CoV-2 B.1.1.7 variant and reinfections in Qatar: a nationally representative cohort study.*PLoS Med* (2021) 18(12):e1003879. Epub 2021/12/17. doi: 10.1371/journal.pmed.1003879.

146. Chemaitelly H, Bertollini R, Abu-Raddad LJ. Efficacy of natural immunity against SARS-CoV-2 reinfection with the beta variant. *N Engl J Med* (2021) 385(27):2585–6. Epub 2021/12/16. doi:

10.1056/NEJMc2110300.

147. Nordström P, Ballin M, Nordström A. Risk of SARS-CoV-2 reinfection and COVID-19 hospitalisation in individuals with natural and hybrid immunity: a retrospective, total population cohort study in Sweden.*Lancet Infect Dis* (2022) 22(6):781–90. Epub 2022/04/04. doi: 10.1016/s1473-3099(22)00143-8.

148. Altarawneh HN, Chemaitelly H, Hasan MR, Ayoub HH, Qassim S, AlMukdad S, et al. Protection against the omicron variant from previous SARS-CoV-2 infection. *N Engl J Med* (2022) 386(13):1288–90. Epub 2022/02/10. doi: 10.1056/NEJMc2200133.

149. Pulliam JRC, van Schalkwyk C, Govender N, von Gottberg A, Cohen C, Groome MJ, et al. Increased risk of SARS-CoV-2 reinfection associated with emergence of omicron in South Africa. *Science* (2022) 376(6593):eabn4947. Epub 2022/03/16. doi: 10.1126/science.abn4947.

150. Guedes AR, Oliveira MS, Tavares BM, Luna-Muschi A, Lazari CDS, Montal AC, et al. Reinfection rate in a cohort of healthcare workers over 2 years of the COVID-19 pandemic. *Sci Rep* (2023) 13(1):712. Epub 2023/01/14. doi: 10.1038/s41598-022-25908-6.

151. Chemaitelly H, Nagelkerke N, Ayoub HH, Coyle P, Tang P, Yassine HM, et al. Duration of immune protection of SARS-CoV-2 natural infection against reinfection. *J Travel Med* (2022) 29(8):taac109. Epub 2022/10/01. doi: 10.1093/jtm/taac109.

152. Bowe B, Xie Y, Al-Aly Z. Acute and postacute sequelae associated with SARS-CoV-2 reinfection. *Nature Medicine* (2022) 28(11):2398–405. doi: 10.1038/s41591-022-02051-3.

153. Yang SL, Ripen AM, Lee JV, Koh K, Yen CH, Chand AK, et al. Time from last immunity event against infection during Omicron-dominant period in Malaysia. *Int J Infect Dis* (2023) 128:98–101. Epub 2022/12/30. doi: 10.1016/j.ijid.2022.12.025.

154. Stein C, Nassereldine H, Sorensen RJD, Amlag JO, Bisignano C, Byrne S, et al. Past SARS-CoV-2 infection protection against re-infection: a systematic review and meta-analysis. *Lancet* (2023). doi: 10.1016/S0140-6736(22)02465-5.

Table 1: Selection of peer-reviewed publications assessing reinfection or risk of severe COVID-19 after natural infection (ordered by study end date, earliest to most recent)

	Study	**Study**	**Study**	**Outcome measures of protection or risk**	**Outcome measures of protection or risk**	**Outcome measures of protection or risk**
	Total size (enrolled; before exclusions)	**Time period**	**Reported lineage**	**Reported outcome measure (protection, risk, reinfection rate)**	**Repeat infection outcome (selected comparisons, terminology as reported)**	**Severe COVID-19 outcome (selected comparisons, terminology as reported)**
Primary publications	**Primary publications**	**Primary publications**	**Primary publications**	**Primary publications**	**Primary publications**	**Primary publications**

	Study	Study	Study	Outcome measures of protection or risk	Outcome measures of protection or risk	Outcome measures of protection or risk
Hansen et al. 2021 Non-vaccinated individuals Denmark (141)	˜ 4 million individuals	Feb 26, 2020–Dec 31, 2020	None	Protection	*Protection against repeat infection in those*11Derived as 1- adjusted relative risk. The rates of infection during the second surge were compared across those with a positive or negative PCR test from the first surge. The calculated the rate of infection was calculated as the number of individuals with positive PCR tests during the second surge divided by the cumulative number of person-days at risk $<$ 65 years: 80.5% (95% CI 75.4–84.5) [?] 65 years: 47.1% (96% CI 24.7–62.8)	Not assessed

	Study	Study	Study	Outcome measures of protection or risk	Outcome measures of protection or risk	Outcome measures of protection or risk
Abu-Raddad et al. 2021 Non-vaccinated individuals22Qatar launched its vaccination campaign on December 21, 2020, around the time this study was concluded (December 31, 2020), so very few individuals had been vaccinated at time of this study. Qatar (142)	192,984 individuals	April 16, 2020–Dec 31, 2020	None	Protection	*Efficacy of natural infection against reinfection*33Derived as 1- the ratio of the incidence rate of reinfection in the antibody-positive cohort to the incidence rate of infection in the antibody-negative cohort. 95.2% (95% CI: 94.1–96.0)	Not assessed Of 129 cases with good or some evidence of reinfection, one reinfection was severe, two were moderate, and none were critical or fatal
Hall et al. 2021 Non-vaccinated and vaccinated individuals UK (143)	30,625 individuals	June 18, 2020–Jan 11, 2021	Not specified B.1.1.7	Risk	*Risk of reinfection causing*44Derived as 1- adjusted incident rate ratio. COVID-19 symptoms: aIRR 0.074 (95% CI 0.06–0.10) All events (COVID-19 symptoms, other symptoms, asymptomatic): aIRR 0.159 (95% CI 0.13–0.19)	Not assessed

	Study	Study	Study	Outcome measures of protection or risk	Outcome measures of protection or risk	Outcome measures of protection or risk
Lumley et al. 2022 Non-vaccinated and vaccinated individuals UK (144)	13,109 individuals	March 27, 2020–Feb 28, 2021	Non-S-gene target failure B.1.1.7	Risk	*Risk of PCR-positive result (symptomatic or asymptomatic) in* Unvaccinated seroposi-tive55Compared incidence in each follow-up group to unvaccinated seronegative healthcare workers.: aIRR 0.02 (95% CI 0.01–0.18)	Not assessed

	Study	Study	Study	Outcome measures of protection or risk	Outcome measures of protection or risk	Outcome measures of protection or risk
Abu-Raddad et al. 2021 Non-vaccinated and vaccinated individuals Qatar (145)	193,233 individuals	Before Nov 1, 2020–March 3, 2021	B.1.1.7 Variants of unknown status	Protection	*Efficacy of natural infection against reinfection with*66Derived as 1- the ratio of the incidence rate of reinfection in the PCR-confirmed (or antibody-positive) cohort to the incidence rate of infection in the antibody-negative cohort. B.1.1.7, prior PCR-confirmed infection: 97.5% (95% CI 95.7–98.6) B.1.1.7, prior antibody-positive result: 97.0% (95% CI 92.5–98.7) Unknown variant, prior PCR-confirmed infection: 92.2% (95% CI: 90.6–93.5) Unknown variant, prior antibody-positive result: 94.2% (95% CI: 91.8–96.0)	Not assessed

	Study	Study	Study	Outcome measures of protection or risk	Outcome measures of protection or risk	Outcome measures of protection or risk
Chemaitelly, H et al. 2021 Unvaccinated individuals (146) Qatar	380,914 individuals	Before Jan 1, 2021–April 21, 202177This timeframe coincided with the beginning of the decline of the B.1.1.7 wave and the rapid expansion of the B.1.351 wave that peaked early April 2021.	B.1.351 B.1.1.7 Variants of unknown status	Protection	*Efficacy of natural infection against reinfection with*88Derived as 1- the ratio of the incidence rate of reinfection in the cohort of individuals with a prior PCR-confirmed infection to the incidence rate of infection in the antibody-negative cohort. B.1.351: 92.3% (95% CI: 90.3–93.8) B.1.1.7: 97.6% (95% CI 95.7–98.7) Variants of unknown status: 87.9% (95% CI: 84.7–90.5)	Not assessed

	Study	Study	Study	Outcome measures of protection or risk	Outcome measures of protection or risk	Outcome measures of protection or risk
Nordström et al. 2022 Non-vaccinated and vaccinated individuals Sweden (147)	˜3.5 million individuals (3 cohorts)	March 20, 2020–Sept 5, 2021	Alpha B.1.1.7 Beta B.1.351 Gamma P.1 Delta B.1.617.2	Risk	*Risk of reinfection in those with* Natural immunity99Calculated vs no immunity and after 3 months of follow-up.: aHR 0.05 (95% CI 0.05–0.05) One-dose hybrid immunity1010Calculated vs natural immunity and during the first 2 months of follow-up.: aHR 0.42 (95% CI 0.38–0.47) One-dose hybrid immunity1111Calculated vs natural immunity and after 2 months of follow-up.: aHR 0.55 (95% CI 0.39–0.76) Two-dose hybrid immunity, overall1212Calculated vs natural immunity.: aHR 0.34 (95% CI 0.31–0.39)	*Risk of hospitalization (HR)* Two-dose hybrid immunity1313Calculate vs natural immunity.: 0.10 (95% CI 0.04–0.22)

	Study	Study	Study	Outcome measures of protection or risk	Outcome measures of protection or risk	Outcome measures of protection or risk
Altarawneh et al. 2022 Non-vaccinated and vaccinated individuals Qatar (148)	˜2.3 million individuals	March 23, 2021–Nov 18, 2021	Alpha Beta Delta Omicron	Protection	*Effectiveness of previous infection in preventing reinfection with*1414Derived as 1- odds ratio of prior infection in cases (PCR-positive persons with variant infection) versus controls (PCR-negative persons)*)* Alpha: 90.2% (95% CI 60.2–97.6) Beta: 85.7% (95% CI 75.8–to 91.7) Delta: 92.0% (95% CI 87.9–94.7) Omicron: 56.0% (95% CI 50.6– 60.9)	*Effectiveness of previous infection in preventing severe, critical or fatal disease caused by* Alpha: 69.4% (95% CI -143.6–96.2) Beta: 88.0% (95% CI 50.7–97.1) Delta: 100% (95% CI 43.3–100) Omicron: 87.8% (95% CI 47.5–97.1)

	Study	Study	Study	Outcome measures of protection or risk	Outcome measures of protection or risk	Outcome measures of protection or risk
Pulliam et al. 2022 Non-vaccinated and vaccinated individuals South Africa (149)	˜2.9 million individuals	March 4, 2020–Jan 31, 2022	Beta (B.1.351) Delta (B.1.617.2) Omicron (B.1.1.529)1515Period of Omicron emergence: November 1, 2021 to November 30, 2021.	Risk	*Risk of reinfection dur-ing*1616Estimated relative hazard ratios for reinfection during specified wave versus primary infection during the first wave. Wave 2 (Beta-driven) versus Wave 1: relative HR 0.71 (95% CI 0.60–0.85) Wave 3 (Delta-driven) versus Wave 1: relative HR 0.54 (95% CI 0.45–0.64) Wave 4 (Omicron-driven) versus Wave 1: relative 1.70 (95% CI 1.44–2.04)	Not assessed

	Study	Study	Study	Outcome measures of protection or risk	Outcome measures of protection or risk	Outcome measures of protection or risk
Guedes et al. 2023 Non-vaccinated and vaccinated individuals Brazil (150)	25,750 real-time RT-PCR tests performed	March 10, 2020–March 20, 2022	Pre-VOC Gamma Delta Omicron	Reinfection rate	*Reinfection rate during the Omicron variant period:* 1717Calculated as number of reinfection cases before and after the Omicron variant considering the total accumulated number of SARS-CoV-2 infections in both periods. Before 0.8% vs after 4.3%; $p<0.001$	Not assessed 281/281 reinfections were mild

	Study	Study	Study	Outcome measures of protection or risk	Outcome measures of protection or risk	Outcome measures of protection or risk
Chemaitelly et al. 2022 (151) Unvaccinated individuals Qatar	Up to 3.3 million individuals	Feb 28, 2020–June 5, 20221818Three individual studies (pre-Omicron reinfection, Omicron reinfection, COVID-19 severity reinfection) spanning different time periods.	Pre-Omicron (ancestral, Alpha, Beta, Delta) Omicron (BA.1, BA.2, BA.4, BA.5)	Protection	*Effectiveness of pre-Omicron primary infection*1919Derived as 1-adjusted hazard ratio, where the hazard ratio compared incidence of infection in both cohorts. Incidence rate of infection in each cohort defined as the number of identified infections divided by the number of person-weeks contributed by all individuals in the cohort. Against pre-Omicron reinfection: 85.5% (95% CI: 84.8–86.2%) Effectiveness peaked at 90.5% (95% CI 88.4–92.3%) in the 7th month after the primary infection, waning to ˜70% by the 16th month Against Omicron reinfection: 38.1% (95% CI 36.3–39.8%), declining with time since primary infection	*Effectiveness of pre-Omicron primary infection*2020Cox regression analysis. Severity, criticality, and fatality defined as per WHO guidelines. Against severe, critical or fatal COVID-19 due to Omicron reinfection: 88.6% (95% CI 70.9–95.5) Against severe, critical, or fatal COVID-19 reinfection (irrespective of the variant of primary infection or reinfection): 97.3% (95% CI 94.9–98.6)

	Study	Study	Study	Outcome measures of protection or risk	Outcome measures of protection or risk	Outcome measures of protection or risk
Bowe et al. 2022 Non-vaccinated and vaccinated individuals USA (152)	˜ 5.8 million individuals	March 1, 2020–June 25, 2022	Pre-Delta Delta Omicron	Risk	Not assessed	*Risk of all-cause mortality (HR)*2121Calcula for reinfection vs no reinfection. 2.17 (95% CI 1.93–2.45) *Risk of hospitalization (HR)* 3.32 (95% CI 3.13–3.51)
Yang et al. 2023 Non-vaccinated and vaccinated individuals Malaysia (153)	482 individuals	Jan 31, 2022–Jul 31, 20222222The Omicron-dominant period in Malaysia was estimated to start from early February 2022.	Non-Omicron Omicron	Risk	*Risk of reinfection in those with* Pre-Omicron natural infection2323Calculated vs Omicron-dominant period.: aHR 0.41 (95% CI 0.27–0.62)	Not assessed
Meta-analyses						

	Study	Study	Study	Outcome measures of protection or risk	Outcome measures of protection or risk	Outcome measures of protection or risk
Stein et al 2023. Global systematic review and meta-analysis of 65 studies from 19 countries (154)	Various	Up to Sept 31, 2022	Ancestral Mixed Alpha (B.1.1.7) Beta (B.1.351) Delta (B.1.617.2) Omicron BA.1 variants	Protection	*Pooled estimate of protection from past infection (with various variants) against reinfection with* Ancestral: 84.9 (95% UI 72.8–91.8) Alpha: 90.0% (95% UI 54.8–98.4) Beta: 85.7% (95% UI 83.4–87.7) Delta: 82.0 (95% UI 63.5–91.9) Omicron BA.1: 45.3% (95% UI 17.3–76.1)	*Pooled estimate of protection against severe disease caused by* Ancestral: 78.1% (95% UI 34.4–96.5) Alpha: 79.6% (95% UI 43.3–95.3) Beta: 88% (95% UI 50.7–97.1)2424Single study. Delta: 97.2% (95% UI 85.2–99.6) Omicron BA.1: 81.9% (95% UI 73.8–88.0)

aRR, adjusted risk ratio; aIRR, adjusted incidence risk ratio; aHR, adjusted hazard ratio; CI, confidence interval; HR, hazard ratio; OR, odds ratio; PE_S, effectiveness of prior infection in preventing reinfection; real-time RT-PCR, real-time reverse transcription polymerase chain reaction; UI, uncertainty interval.