RESEARCH PUBLICATIONS

Antibody and B cell responses to SARS-CoV-2 infection and vaccination

Abstract

Antibodies, and the B cell and plasma cell populations responsible for their production, are key components of the human immune system's response to SARS-CoV-2, which has caused the coronavirus disease 2019 (COVID-19) pandemic. Here, findings addressing reviewed the nature of antibody responses against SARS-CoV-2 and their role in protecting from infection or modulating COVID-19 disease severity. In just over a year, much has been learned, and replicated in independent studies, about human immune responses to this pathogen, contributing to the development of effective vaccines. Nevertheless, important questions remain about the duration and effectiveness of antibody responses, differences between immunity derived from infection compared to vaccination, the cellular basis for serological findings, and the extent to which viral variants will escape from current immunity.

Reference

https://www.cell.com/cell-host-microbe/fulltext/S1931-3128%2821%2900287-0

Dissecting the common and compartment-specific features of COVID-19 severity in the lung and periphery with single-cell resolution

Abstract

Severe COVID-19 is accompanied by rampant immune dysregulation in the lung and periphery, with immune cells of both compartments contributing to systemic distress. The extent to which immune cells of the lung and blood enter similar or distinct pathological states during severe disease remains unknown. Here, 96 publicly available

single-cell RNA sequencing datasets were leveraged to elucidate common and compartment-specific features of severe to critical COVID-19 at the levels of transcript expression, biological pathways, and ligand-receptor signaling networks. Comparing severe patients to milder and healthy donors, distinct differential gene expression signatures were identified between compartments and a core set of co-directionally regulated surface markers. A majority of severity-enriched pathways were shared, whereas TNF and interferon responses were polarized. Severity-specific ligand-receptor networks appeared to be differentially active in both compartments. Overall, the results describe a nuanced response during severe COVID-19 where compartment plays a role in dictating the pathological state of immune cells.

Reference

https://www.cell.com/iscience/fulltext/S2589-0042%2821%2900706-9

Reduced neutralization of SARS-CoV-2 B.1.617 by vaccine and convalescent serum

Abstract

SARS-CoV-2 has undergone progressive change with variants conferring advantage rapidly becoming dominant lineages e.g. B.1.617. With apparent increased transmissibility variant B.1.617.2 has contributed to the current wave of infection ravaging the Indian subcontinent and has been designated a variant of concern in the UK. Here the ability of monoclonal antibodies was studied, convalescent and vaccine sera to neutralize B.1.617.1 and B.1.617.2 and complement this with structural analyses of Fab/RBD complexes and map the antigenic space of current variants. Neutralization of both viruses is reduced when compared with ancestral Wuhan related strains but there is no evidence of widespread antibody escape as seen with B.1.351. However, B.1.351 and P.1 sera showed markedly more reduction in neutralization of B.1.617.2 suggesting that individuals previously infected by these variants may be more susceptible to reinfection by B.1.617.2. This observation provides important new insight for immunisation policy with future variant vaccines in non-immune populations.

Reference

https://www.cell.com/cell/fulltext/S0092-8674%2821%2900755-8

Sintilimab plus a bevacizumab biosimilar (IBI305) versus sorafenib in unresectable hepatocellular carcinoma (ORIENT-32): A randomised, open-label, phase 2–3 study

Abstract

Background: China has a high burden of hepatocellular carcinoma, and hepatitis B virus (HBV) infection is the main causative factor. Patients with hepatocellular carcinoma have a poor prognosis and a substantial unmet clinical need. The phase 2–3 ORIENT-32 study aimed to assess sintilimab (a PD-1 inhibitor) plus IBI305, a bevacizumab biosimilar, versus sorafenib as a first-line treatment for unresectable HBV-associated hepatocellular carcinoma.

Methods: This randomised, open-label, phase 2–3 study was done at 50 clinical sites in China. Patients aged 18 years or older with histologically or cytologically diagnosed or clinically confirmed unresectable or metastatic hepatocellular carcinoma, no previous systemic treatment, and a baseline Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 were eligible for inclusion. In the phase 2 part of the study, patients received intravenous sintilimab (200 mg every 3 weeks) plus intravenous IBI305 (15 mg/kg every 3 weeks). In the phase 3 part, patients were randomly assigned (2:1) to receive either sintilimab plus IBI305 (sintilimab–bevacizumab biosimilar group) or sorafenib (400 mg orally twice daily; sorafenib group), until disease progression or unacceptable toxicity. Randomisation was done using permuted block randomisation, with a block size of six, via an interactive web response system, and stratified by macrovascular invasion or extrahepatic metastasis, baseline α-fetoprotein, and ECOG performance status. The primary endpoint of the phase 2 part of the study was safety, assessed in all patients who received at least one dose of study drug. The co-primary endpoints of the phase 3 part of the study were overall survival and independent radiological review committee (IRRC)-assessed progression-free survival according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 in the intention-to-treat population. The study is registered with ClinicalTrials.gov, NCT03794440. The study is closed to new participants and follow-up is ongoing for long-term outcomes.

Findings: Between Feb 11, 2019 and Jan 15, 2020, we enrolled 595 patients: 24 were enrolled directly into the phase 2 safety run-in and 571 were randomly assigned to sintilimab–bevacizumab biosimilar (n=380) or sorafenib (n=191). In the phase 2 part of the trial, 24 patients received at least one dose of the study drug, with an objective response rate of 25·0% (95% CI 9·8–46·7). Based on the preliminary safety and activity data of the phase 2 part, in which grade 3 or worse treatment-related adverse events occurred in seven (29%) of 24 patients, the randomised phase 3 part was started. At data cutoff (Aug 15, 2020), the median follow-up was 10·0 months (IQR 8·5–11·7) in the sintilimab–bevacizumab biosimilar group and 10·0 months (8·4–11·7) in the sorafenib group. Patients in the sintilimab–bevacizumab biosimilar group had a significantly longer IRRC-assessed median progression-free survival (4·6 months [95% CI 4·1–5·7]) than did patients in the sorafenib group (2·8 months [2·7–3·2]; stratified hazard ratio [HR] 0·56, 95% CI 0·46–0·70; p<0·0001). In the first interim analysis of overall survival, sintilimab–bevacizumab biosimilar showed a significantly longer overall survival than did sorafenib (median not reached [95% CI not reached–not reached] vs 10·4 months [8·5–not reached]; HR 0·57, 95% CI 0·43–0·75; p<0·0001). The most common grade 3–4 treatment-emergent adverse events were hypertension (55 [14%] of 380 patients in the sintilimab–bevacizumab biosimilar group vs 11 [6%] of 185 patients in the sorafenib group) and palmar-plantar erythrodysaesthesia syndrome (none vs 22 [12%]). 123 (32%) patients in the sintilimab–bevacizumab biosimilar group and 36 (19%) patients in the sorafenib group had serious adverse events. Treatment-related adverse events that led to death occurred in six (2%) patients in the sintilimab–bevacizumab biosimilar group (one patient with abnormal liver function, one patient with both hepatic failure and gastrointestinal haemorrhage, one patient with interstitial lung disease, one patient with both hepatic faliure and hyperkalemia, one patient with upper gastrointestinal haemorrhage, and one patient with intestinal volvulus) and two (1%) patients in the sorafenib group (one patient with gastrointestinal haemorrhage and one patient with death of unknown cause).

Interpretation: Sintilimab plus IBI305 showed a significant overall survival and progression-free survival benefit versus sorafenib in the first-line setting for Chinese patients with unresectable, HBV-associated hepatocellular carcinoma, with an acceptable safety profile. This combination regimen could provide a novel treatment option for such patients.

Reference

https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(21)00252-7/fulltext

Naturally enhanced neutralizing breadth against SARS-CoV-2 one year after infection

Abstract

More than one year after its inception, the coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) remains difficult to control despite the availability of several working vaccines. Progress in controlling the pandemic is slowed by the emergence of variants that appear to be more transmissible and more resistant to antibodies. Here it was reported on a cohort of 63 individuals who have recovered from COVID-19 assessed at 1.3, 6.2 and 12 months after SARS-CoV-2 infection, 41% of whom also received mRNA vaccines. In the absence of vaccination, antibody reactivity to the receptor binding domain (RBD) of SARS-CoV-2, neutralizing activity and the number of RBD-specific memory B cells remain relatively stable between 6 and 12 months after infection. Vaccination increases all components of the humoral response and, as expected, results in serum neutralizing activities against variants of concern similar to or greater than the neutralizing activity against the original Wuhan Hu-1 strain achieved by vaccination of naive individuals. The mechanism underlying these broad-based responses involves ongoing antibody somatic mutation, memory B cell clonal turnover and development of monoclonal antibodies that are exceptionally resistant to SARS-CoV-2 RBD mutations, including those found in the variants of concerns. In addition, B cell clones expressing broad and potent antibodies are selectively retained in the repertoire over time and expand markedly after vaccination. The data suggest that immunity in convalescent individuals will be very long lasting and that convalescent individuals who receive available mRNA vaccines will produce antibodies and memory B cells that should be protective against circulating SARS-CoV-2 variants.

Reference

https://www.nature.com/articles/s41586-021-03696-9

Serological analysis reveals an imbalanced IgG subclass composition associated with COVID-19 disease severity

Abstract

Coronavirus disease 2019 (COVID-19) is associated with a wide spectrum of disease presentation, ranging from asymptomatic infection to acute respiratory distress syndrome (ARDS). Paradoxically, a direct relationship has been suggested between COVID-19 disease severity and the levels of circulating severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-specific antibodies, including virus-neutralizing titers. A serological analysis of 536 convalescent healthcare workers reveals that SARS-CoV-2-specific and virus-neutralizing antibody levels are elevated in individuals that experience severe disease. The severity-associated increase in SARS-CoV-2-specific antibody is dominated by immunoglobulin G (IgG), with an IgG subclass ratio skewed toward elevated receptor binding domain (RBD)- and S1-specific IgG3. In addition, individuals that experience severe disease show elevated SARS-CoV-2-specific antibody binding to the inflammatory receptor FcγRIIIa. Based on these correlational studies, we propose that spike-specific IgG subclass utilization may contribute to COVID-19 disease severity through potent Fc-mediated effector functions. These results may have significant implications for SARS-CoV-2 vaccine design and convalescent plasma therapy.

Reference

https://www.cell.com/cell-reports-medicine/fulltext/S2666-3791%2821%2900172-5

A time-resolved proteomic and prognostic map of COVID-19

Abstract

COVID-19 is highly variable in its clinical presentation, ranging from asymptomatic infection to severe organ damage and death. The time-dependent progression of the disease were characterized in 139 COVID-19 inpatients by measuring 86 accredited diagnostic parameters, such as blood cell counts and enzyme activities, as well as untargeted plasma proteomes at 687 sampling points. An initial spike was reported in a systemic inflammatory response, which is gradually alleviated and followed by a protein signature indicative of tissue repair, metabolic reconstitution, and immunomodulation.

Prognostic marker signatures were identified for devising risk-adapted treatment strategies and use machine learning to classify therapeutic needs. It was shown that the machine learning models based on the proteome are transferable to an independent cohort. The study presents a map linking routinely used clinical diagnostic parameters to plasma proteomes and their dynamics in an infectious disease.

Reference

https://www.cell.com/cell-systems/fulltext/S2405-4712%2821%2900160-5

SARS-CoV-2 spike L452R variant evades cellular immunity and increases infectivity

Abstract

Many SARS-CoV-2 variants with naturally acquired mutations have emerged. These mutations can affect viral properties such as infectivity and immune resistance. Although the sensitivity of naturally occurring SARS-CoV-2 variants to humoral immunity has been investigated, sensitivity to human leukocyte antigen (HLA)-restricted cellular immunity remains largely unexplored. Here, it was demonstrated that two recently emerging mutations in the receptor-binding domain of the SARS-CoV-2 spike protein, L452R (in B.1.427/429 and B.1.617) and Y453F (in B.1.1.298), confer escape from HLA-A24-restricted cellular immunity. These mutations reinforce affinity toward the host entry receptor ACE2. Notably, the L452R mutation increases spike stability, viral infectivity, viral fusogenicity, and thereby promotes viral replication. These data suggest that HLA-restricted cellular immunity potentially affects the evolution of viral phenotypes and that a further threat of the SARS-CoV-2 pandemic is escape from cellular immunity.

Reference

https://www.cell.com/cell-host-microbe/fulltext/S1931-3128%2821%2900284-5

Memory B cells targeting SARS-CoV-2 spike protein and their dependence on CD4+ T cell help

Abstract

Memory B cells seem to be more durable than antibodies and thus crucial for the long-term immunity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Here SARS-CoV-2 spike-specific memory B cells were investigated and their dependence on CD4+ T cell help in different settings of coronavirus disease 2019 (COVID-19). Compared with severely ill individuals, those who recovered from mild COVID-19 develop fewer but functionally superior spike-specific memory B cells. Generation and affinity maturation of these cells is best associated with IL-21+CD4+ T cells in recovered individuals and CD40L+CD4+ T cells in severely ill individuals. The increased activation and exhaustion of memory B cells observed during COVID-19 correlates with CD4+ T cell functions. Intriguingly, CD4+ T cells recognizing membrane protein show a stronger association with spike-specific memory B cells than those recognizing spike or nucleocapsid proteins. Overall, CD4+ T cell subsets were identified, which were associated with the generation of B cell memory during SARS-CoV-2 infection.

Reference

https://www.cell.com/cell-reports/fulltext/S2211-1247%2821%2900696-3

Distinct clinical and immunological profiles of patients with evidence of SARS-CoV-2 infection in sub-Saharan Africa

Abstract

Although the COVID-19 pandemic has left no country untouched there has been limited research to understand clinical and immunological responses in African populations. Here patients hospitalised was characterized with suspected (PCR-negative/IgG-positive) or confirmed (PCR-positive) COVID-19, and healthy community controls (PCR-negative/IgG-negative). PCR-positive COVID-19 participants were more likely to receive dexamethasone and a *beta*-lactam antibiotic, and survive to hospital discharge than PCR-negative/IgG-positive and PCR-negative/IgG-negative participants. PCR-

negative/IgG-positive participants exhibited a nasal and systemic cytokine signature analogous to PCR-positive COVID-19 participants, predominated by chemokines and neutrophils and distinct from PCR-negative/IgG-negative participants. PCR-negative/IgG-positive participants had increased propensity for *Staphylococcus aureus* and *Streptococcus pneumoniae* colonisation. PCR-negative/IgG-positive individuals with high COVID-19 clinical suspicion had inflammatory profiles analogous to PCR-confirmed disease and potentially represent a target population for COVID-19 treatment strategies.

Reference

https://www.nature.com/articles/s41467-021-23267-w

Development of a sensitive and reproducible cell-based assay using secNanoLuc to detect neutralizing antibody against adeno-associated virus vector capsid

Abstract

Most gene therapy clinical trials that systemically administered adeno-associated virus (AAV) vector enrolled only patients without anti-AAV-neutralizing antibodies. However, laboratory tests to measure neutralizing antibodies varied among clinical trials and have not been standardized. Here, it was attempted to improve the sensitivity and reproducibility of a cell-based assay to detect neutralizing antibodies and to determine the detection threshold to predict treatment efficacy. Application of the secreted type of NanoLuc and AAV receptor-expressing cells reduced the multiplicity of infection (m.o.i.) for AAV transduction and improved the sensitivity to detect neutralizing antibodies with low coefficient of variation, whereas detection threshold could not be improved by the reduction of m.o.i. to <100. After human immunoglobulin administration into mice at various doses, treatment with high-dose AAV8 vector enabled evasion of the inhibitory effect of neutralizing antibodies. Conversely, gene transduction was slightly influenced in the mice treated with low-dose AAV8 vector, even when neutralizing antibodies were determined to be negative in the assay. In conclusion, we developed a reliable and sensitive cell-based assay to measure neutralizing antibodies against AAV and found that the appropriate m.o.i. to detect marginal neutralizing antibodies was 100. Other factors, including noninhibitory antibodies, marginally influence in vivo transduction at low vector doses.

Reference

Discontinuation versus continuation of renin-angiotensin-system inhibitors in COVID-19 (ACEI-COVID): A prospective, parallel group, randomised, controlled, open-label trial

Abstract

Background: SARS-CoV-2 entry in human cells depends on angiotensin-converting enzyme 2, which can be upregulated by inhibitors of the renin–angiotensin system (RAS). It was aimed to test our hypothesis that discontinuation of chronic treatment with ACE-inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) mitigates the course o\f recent-onset COVID-19.

Methods: ACEI-COVID was a parallel group, randomised, controlled, open-label trial done at 35 centres in Austria and Germany. Patients aged 18 years and older were enrolled if they presented with recent symptomatic SARS-CoV-2 infection and were chronically treated with ACEIs or ARBs. Patients were randomly assigned 1:1 to discontinuation or continuation of RAS inhibition for 30 days. Primary outcome was the maximum sequential organ failure assessment (SOFA) score within 30 days, where death was scored with the maximum achievable SOFA score. Secondary endpoints were area under the death-adjusted SOFA score (AUCSOFA), mean SOFA score, admission to the intensive care unit, mechanical ventilation, and death. Analyses were done on a modified intention-to-treat basis. This trial is registered with ClinicalTrials.gov, NCT04353596.

Findings: Between April 20, 2020, and Jan 20, 2021, 204 patients (median age 75 years [IQR 66–80], 37% females) were randomly assigned to discontinue (n=104) or continue (n=100) RAS inhibition. Within 30 days, eight (8%) of 104 died in the discontinuation group and 12 (12%) of 100 patients died in the continuation group (p=0·42). There was no significant difference in the primary endpoint between the discontinuation and continuation group (median [IQR] maximum SOFA score 0·00 (0·00–2·00) vs 1·00 (0·00–3·00); p=0·12). Discontinuation was associated with a significantly lower AUCSOFA (0·00 [0·00–9·25] vs 3·50 [0·00–23·50]; p=0·040), mean SOFA score (0·00

[0·00–0·31] vs 0·12 [0·00–0·78]; p=0·040), and 30-day SOFA score (0·00 [10–90th percentile, 0·00–1·20] vs 0·00 [0·00–24·00]; p=0·023). At 30 days, 11 (11%) in the discontinuation group and 23 (23%) in the continuation group had signs of organ dysfunction (SOFA score ≥1) or were dead (p=0·017). There were no significant differences for mechanical ventilation (10 (10%) vs 8 (8%), p=0·87) and admission to intensive care unit (20 [19%] vs 18 [18%], p=0·96) between the discontinuation and continuation group.

Interpretation: Discontinuation of RAS-inhibition in COVID-19 had no significant effect on the maximum severity of COVID-19 but may lead to a faster and better recovery. The decision to continue or discontinue should be made on an individual basis, considering the risk profile, the indication for RAS inhibition, and the availability of alternative therapies and outpatient monitoring options.

Reference

https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(21)00214-9/fulltext

Publication Date: Jun 10, 2021

Clinical characteristics and risk factors for death among hospitalised children and adolescents with COVID-19 in Brazil: an analysis of a nationwide database

Abstract

Background: COVID-19 is usually less severe and has lower case fatality in children than in adults. It was aimed to characterize the clinical features of children and adolescents hospitalized with laboratory-confirmed SARS-CoV-2 infection and to evaluate the risk factors for COVID-19-related death in this population.

Methods: An analysis of all patients younger than 20 years was done, who had quantitative RT-PCR-confirmed COVID-19 and were registered in the Influenza Epidemiological Surveillance Information System (SIVEP-Gripe, a nationwide surveillance database of patients admitted to hospital with severe acute respiratory disease in Brazil), between Feb 16, 2020, and Jan 9, 2021. The primary outcome was time to recovery (discharge) or in-hospital death, evaluated by competing risks analysis using the cumulative incidence function.

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Findings: Of the 82 055 patients younger than 20 years reported to SIVEP-Gripe during the study period, 11 613 (14·2%) had available data showing laboratory-confirmed SARS-CoV-2 infection and were included in the sample. Among these patients, 886 (7·6%) died in hospital (at a median 6 days [IQR 3–15] after hospital admission), 10 041 (86·5%) patients were discharged from the hospital, 369 (3·2%) were in hospital at the time of analysis, and 317 (2·7%) were missing information on outcome. The estimated probability of death was 4·8% during the first 10 days after hospital admission, 6·7% during the first 20 days, and 8·1% at the end of follow-up. Probability of discharge was 54·1% during the first 10 days, 78·4% during the first 20 days, and 92·0% at the end of follow-up. The competing risks multivariate survival analysis showed that risk of death was increased in infants younger than 2 years (hazard ratio 2·36 [95% CI 1·94–2·88]) or adolescents aged 12–19 years (2·23 [1·84–2·71]) relative to children aged 2–11 years; those of Indigenous ethnicity (3·36 [2·15–5·24]) relative to those of White ethnicity; those living in the Northeast region (2·06 [1·68–2·52]) or North region (1·55 [1·22–1·98]) relative to those in the Southeast region; and those with one (2·96 [2·52–3·47]), two (4·96 [3·80–6·48]), or three or more (7·28 [4·56–11·6]) pre-existing medical conditions relative to those with none.

Interpretation: Death from COVID-19 was associated with age, Indigenous ethnicity, poor geopolitical region, and pre-existing medical conditions. Disparities in health care, poverty, and comorbidities can contribute to magnifying the burden of COVID-19 in more vulnerable and socioeconomically disadvantaged children and adolescents in Brazil.

Reference

https://www.thelancet.com/journals/lanchi/article/PIIS2352-4642(21)00134-6/fulltext

CORRESPONDANCE

Extracorporeal membrane oxygenation for COVID-19 during first and second waves

COVID-19 has ravished the world, with secondary consequences that are not yet possible to estimate. WHO and the European Extracorporeal Life Support Organization (ELSO) recommended extracorporeal membrane oxygenation (ECMO) early in the pandemic, according to the standard criteria. In March, 2020, the EuroELSO survey was established to report the use of ECMO and outcomes in patients with COVID-19 once per week. Several months into the pandemic, we learned empirically that steroids and thromboprophylaxis improved outcome, which was confirmed by subsequent studies. Data from the EuroECMO survey collected between March 12, 2020, and Sept 14, 2020 (ie, the first wave), and other multicentre aggregates showed favourable outcomes with survival of 55–60%. Less encouraging outcomes were also reported, with survival rate of less than 30%.

The continuous provision of ECMO for patients with COVID-19 was analyzed during the first and second waves from the EuroECMO survey. The results indicate that the clinical picture has changed during the second wave (between Sept 15, 2020, and March 8, 2021). Fatality and successful weaning curves approach each other, indicating an increase in mortality compared with weaning and survival (figure 1). An analysis of the deceased to weaned ratio during 2020 shows a significantly increasing trend over time (figure 2). During the spring and early summer of 2020, this ratio was less than 1—ie, the number of weaned (survivors from ECMO) was higher than the number of deceased. Currently, this ratio is more than 1, indicating worse outcome (p<0·006; median–median linear regression). The same pattern emerges concerning survival between first and second waves on the basis of data released on March 8, 2021. In the first wave, successful weaning was accomplished in 58% (841 of 1442) of patients, compared with 47% (718 of 1723; p<0·0001) in the second wave. Including deaths reported after successful weaning, survival was 53% (770) in the first wave and 44% (677; p<0.0001) in the second wave. For more details, read the link given below,

Reference

https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(21)00262-9/fulltext

ChAdOx1 nCoV-19 vaccine: Asymptomatic efficacy estimates

Merryn Voysey and colleagues1 provide some of the first evidence of the effectiveness of ChAdOx1 nCoV-19 vaccine (AZD1222) against asymptomatic infections. However, readers might be surprised by the non-intuitive results reported in the tables, where vaccine efficacy estimates for asymptomatic infections are close to the null or even negative.

Voysey and colleagues suggest that protection against asymptomatic infections is shown by the outcome that includes any nucleic acid amplification test-positive cases. However, there is still value in directly estimating the efficacy against asymptomatic infections. As estimated in table 1 of the Article, this parameter is calculated using the rate ratio that compares asymptomatic infections between the vaccinated and control groups. However, we argue that the rate of asymptomatic infections in the control group is not the appropriate comparator because it requires the implausible assumption that all prevented symptomatic cases were completely averted, rather than converted to asymptomatic infections. If it is instead assumed that all symptomatic infections prevented by the vaccine would become asymptomatic, the appropriate counterfactual would be the rate of asymptomatic infections in the control group plus the rate of symptomatic cases that was averted by vaccine. For more details, read the given link below.

Reference

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00951-X/fulltext