RESEARCH ARTICLE

Prevalence of neutralising antibodies against SARS-CoV-2 in acute infection and convalescence: A systematic review and meta-analysis

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Abstract

Background

Individuals infected with SARS-CoV-2 develop neutralising antibodies. We investigated the proportion of individuals with SARS-CoV-2 neutralising antibodies after infection and how this proportion varies with selected covariates.

Methodology/Principal findings

This systematic review and meta-analysis examined the proportion of individuals with SARS-CoV-2 neutralising antibodies after infection and how these proportions vary with selected covariates. Three models using the maximum likelihood method assessed these proportions by study group, covariates and individually extracted data (protocol CRD42020208913). A total of 983 reports were identified and 27 were included. The pooled (95%CI) proportion of individuals with neutralising antibodies was 85.3% (83.5–86.9) using the titre cut off >1:20 and 83.9% (82.2–85.6), 70.2% (68.1–72.5) and 54.2% (52.0–56.5) with titres >1:40, >1:80 and >1:160, respectively. These proportions were higher among patients with severe COVID-19 (e.g., titres >1:80, 84.8% [80.0–89.2], >1:160, 74.4% [67.5–79.7]) than those with mild presentation (56.7% [49.9–62.9] and 44.1% [37.3–50.6], respectively) and lowest among asymptomatic infections (28.6% [17.9–39.2] and 10.0% [3.7–20.1], respectively). IgG and neutralising antibody levels correlated poorly.

Conclusions/Significance

85% of individuals with proven SARS-CoV-2 infection had detectable neutralising antibodies. This proportion varied with disease severity, study setting, time since infection and the method used to measure antibodies.

Author summary

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) elicits adaptive immunological responses, including immunoglobulins A, M, and G and neutralising antibodies. Neutralising antibodies are considered markers of functional immunity and protection. However, not all individuals with proven infections have detectable neutralising antibodies. In this systematic review, we investigated the proportion of individuals with former SARS-CoV-2 infections who develop neutralising antibodies, whether their titres vary with disease severity, and their correlation with Immunoglobulin G. We found that approximately 85% of individuals with SARS-CoV-2 infection have detectable neutralising antibodies. This proportion was higher among patients with severe Coronavirus Disease 19 and lower in asymptomatic infections. The variation across studies reflected the wide range of methods used to measure both immunoglobulins and neutralising antibodies, and highlight the need for an international reference standard to measure SARS-CoV-2 antibodies.

Introduction

The emergence of Coronavirus Disease 2019 (COVID-19), caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), in December 2019 [1] marked the start of the first global pandemic of this century, resulting in over 34 million cases and 1 million deaths in the following six months [2]. SARS-CoV-2 infection has a wide spectrum of manifestations ranging from asymptomatic infections to a multi-system disease with multi-organ involvement and a high mortality [3]. Its diagnosis is based on the detection of viral RNA using Reverse Transcription Polymerase Chain Reaction (RT-PCR) or rapid antigen tests [4]. SARS-CoV-2 specific assays to detect immunoglobulins (Ig) G, M, and A are well established and individuals with anti-SARS-CoV-2 antibodies are expected to have some degree of protection against infection [5]. However their correlation to functional immunity is poorly described [6].

Functional immunity is better depicted by measuring neutralising antibodies, which bind to viral surface proteins, and prevent cell infection and plaque formation in cell cultures [7]. There is however a wide array of methodologies to measure neutralising antibodies, from employing microscopy to measuring cell metabolism in the presence of virus and antibody. In addition, reporting measures differ between studies, some plot a sigmoid curve and report the viral titres that reduce viral plaques or cell metabolism to 50%, and others report the minimum antibody titre that abolishes all viral activity in cell culture.

Here we present a systematic review and meta-analysis to describe the proportion of individuals who develop SARS-CoV-2 neutralising antibodies after infection, whether this proportion varies with disease severity, the time after symptoms onset, and the correlation between IgG and neutralising antibodies titres.

Methods

This study followed the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [8]. Institutional review board approval and informed consent were not required because all data were obtained from secondary data sources and were de-identified. Similarly, the study used secondary sources of data and was not possible to seek public and patient involvement. The study protocol was registered at PROSPERO (CRD42020208913).

Search strategy and selection criteria

We conducted a systematic search of publications using the PubMed (including MEDLINE), Web of Science, and Cochrane databases, and of preprints in bioRxiv, medRxiv and the Collabovid.org website, which includes a compilation of manuscripts on COVID-19 from arXiv, bioRxiv, Elsevier and medRxiv. The search included reports from 1st January 2020 to 12th August 2020 and was limited to human studies. The search terms used were: "severe acute respiratory coronavirus 2" OR "SARS-CoV-2" OR "sars AND virus" OR "sars AND cov" OR "COVID-19" OR "COVID 2019" OR "novel coronavirus" OR "new coronavirus" OR "Wuhan coronavirus" OR "Coronavirus disease 19" OR "2019-nCoV" AND "neutralising antibod*" OR "neutralizing antibod*" OR "neutralising AND antibod*" OR "neutralizing AND antibod*", without language restrictions (S1 Table). Two reviewers (HRS and TE) independently screened the titles and abstracts and selected full text manuscripts to assess for inclusion. Studies were retained if they had tested for neutralising antibodies against SARS-CoV-2 in participants with laboratory confirmed SARS-CoV-2 infection. We included studies that reported aggregated or individual data or where data could be extracted from graphical displays. We excluded studies without original data, if data could not be extracted, or if the titre cut offs used were not comparable to other studies. Studies including SARS-CoV-2 vaccinated patients or individuals receiving plasma therapy were excluded.

Data extraction and bias assessment

Data were extracted using a pre-piloted extraction form, including author, year, country, study design, setting (hospital, community or plasma donor), age, gender, severity of symptoms (asymptomatic, mild, moderate, severe), and weeks/months elapsed since infection. Laboratory data included the assay used to measure neutralising antibodies, the plaque reduction threshold used to classify participants as having neutralising antibodies, the lower threshold attained, additional titre thresholds used, and the IgG Enzyme linked immunoassay (ELISA) used. Data were extracted from digitised graphs using Engauge software for individual data extraction (http://markummitchell.github.io/engauge-digitizer/). Data were selected using a 50% plaque reduction cut off for neutralising antibody titres (i.e., 50% of the virus in the culture was neutralised by the patient's serum (PRNT50)) or the PRNT90 for one study in which the PRNT50 was not provided. Immunoglobulins usually increase on week after infection and peak after 21 days. Thus, for studies that described a time window for sample collection (i.e., 7–10 days) we recorded the end of the window to generate the most conservative estimate. We extracted data for titre cut offs 1:20, 1:40, 1:80, and 1:160, as these were the dilutions used by most studies.

The NIH Study Quality Assessment tool was used to assess the risk of bias and study quality for case series and cohort studies (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools). Studies were initially rated as having good, fair, or poor quality, and ratings were discussed to reach consensus.

Data analysis

We developed three statistical models in an R software environment to assess 1) the combined proportion of individuals with neutralising antibodies across studies; 2) the correlation between the proportions of participants with IgG and neutralising antibodies and 3) the correlation between individual-level IgG and neutralising antibodies. The meta-analysis combined the proportion of participants with neutralising antibodies across all studies. We used the maximum likelihood method with a quasi-Monte Carlo approximation. Ten thousand samples were simulated using the inverse transformation method by conditioning on different variables that could modify the proportion positive, including disease severity, participant recruitment setting, and neutralising antibody detection method. The resulting proportions were summarised as means and 95% confidence intervals. The correlation between the proportions of participants in a study with IgG and neutralising antibodies was estimated using a quasi-Monte Carlo method for maximum likelihood estimation, adjusting for study setting, titre cut off threshold, and neutralising antibody detection method. The 95% confidence intervals were obtained via parametric bootstraps. The individual correlation model was a bivariate model of individually extracted IgG and neutralising antibody data. Each study was modelled separately because studies used different ELISA and reporting units and did not provide enough background to standardise results. The model was fitted using a maximum likelihood method, with covariates taken from each study. A more detailed description of the statistical methods is available in the supporting information (S1 Text).

Results

The search identified 983 reports. After screening titles and abstracts 78 full-text articles were assessed for eligibility, resulting in 27 studies that met the criteria for inclusion in the analysis (Fig 1). Twelve studies were case series and fifteen cohort studies, as shown in Table 1. Seventeen studies were conducted in hospital settings, three in community or outreach centres, and seven were based on plasma donors. Thirteen studies included hospitalised and eleven convalescent patients. Only one study included children. IgG was assessed using eleven in-house and 16 commercial ELISAs. Neutralising antibodies were detected using the Focus Reduction Neutralisation Test (FRNT) by two studies, the PRNT by five studies, the Virus Neutralisation Test (VNT) by three studies, the surrogate VNT by one study, the pseudovirus VNT by nine studies and the microneutralisation method by seven studies.

The risk of bias in the studies is shown in the supporting information (S2 Table). The main risk identified was the lack of sample size estimations, as only two studies included pre-study sample size estimations, and sample sizes were usually based on the number of cases or samples available. None of the studies reported blinding of the endpoints. Four studies were considered to have fair and 23 to have good study quality.

Proportion of participants with SARS-CoV-2 neutralising antibodies

Eighteen studies reported the proportion of participants with SARS-CoV-2 neutralising antibodies with titres >1:20 [9–26], 18 reported titres >1:40 [9–12,14,16,17,19–22,25,27–32],17 reported titres >1:80 [9–12,14,16,17,19–22,25,27,29,33–35], and 18 reported titres >1:160 [9–12,14–17,19–22,25,27,29,32–34]. The pooled proportion of participants with neutralising antibodies varied with the titre threshold used (Fig 2) and ranged from 85.3% (95%CI 83.5 to 86.9) in studies using threshold titres >1:20; 83.9% (95%CI 82.2 to 85.6) with titres >1:40, and 70.2% (95%CI 68.1 to 72.5) and 54.2% (52.0 to 56.5) with titres >1:80 and >1:160, respectively (Table 2).

Fig 1. Flow diagram of study selection.

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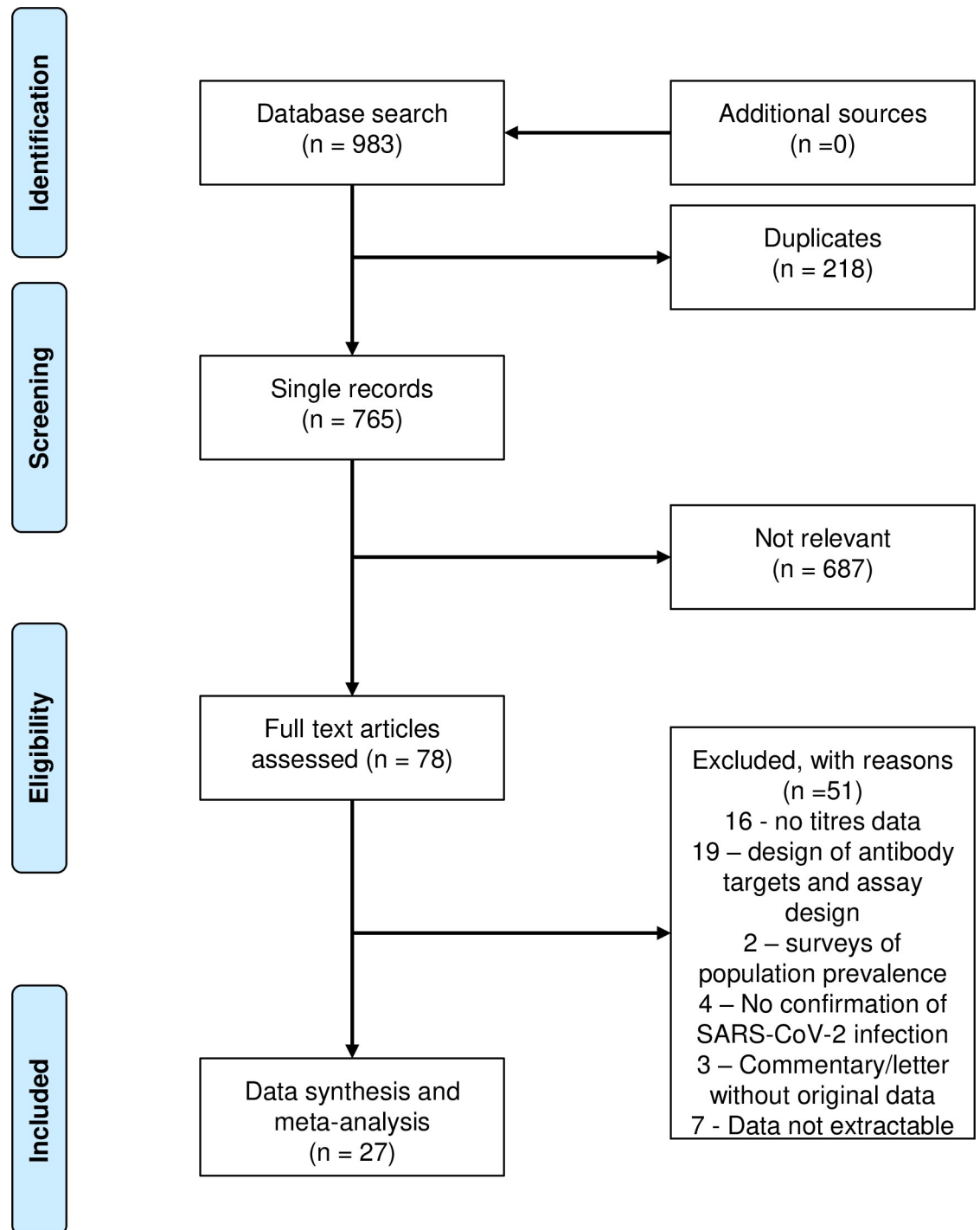
The proportion of participants classified as having neutralising antibodies varied with the detection method, with the pseudovirus method reporting the highest and the microneutralisation method the lowest proportion of participants detectable (titre threshold >1:20, 94.9% [95%CI 90.2 to 98.0] and 66.8% [95%CI 55.0 to 75.2], respectively), with similar differences

Table 1. Study characteristics of the 27 studies included.

Author	Country	Study design	Setting	Participants	Disease Severity*	IgG Assay*	Target	Neutralising Antibody method	Sample size
Brochot et al	France	Cohort	H	Inpatient	M/S	ELISA IH	S1, S2, N, RBD	Pseudovirus VNT	30
Tang et al	USA	Cohort	H	Inpatient	M/S	Euroimmun Roche Abbott	S1 S N	FRNT	48
Kohmer et al	Germany	Case series	H	Inpatient	M/S	Euroimmun Vircell	S1 S, N	PRNT	45
Bonelli et al	Italy	Cohort	H	Inpatient/ Community	M/S	Diasorin	S1, S2	Microneutralisation	304
Kohmer, Westhaus et al	Germany	Case series	H	Inpatient	S	Abbott Virotech Vircell	N N N	PRNT	33
Suhandynata et al	USA	Cohort	C	Convalescent	A	Abbott Roche Diazyme	N N, S n/a	Pseudovirus VNT	63
Zhang et al	China	Case series	H	Convalescent	M/S	ELISA IH1 IH2	S1 S2	Pseudovirus VNT	67
Stromer et al	Germany	Case series	PD	Convalescent	M/Md/S	Abbott Roche Dyazyme Mikrogen Epitope diagnostics Euroimmun	N N N, S N N S1	PRNT	26
Liu et al	China	Case series	H	Paediatric	M/S	n/a	n/a	Pseudovirus VNT	9
Crawford et al	USA	Cohort	H/C	Convalescent	A/M/Md	ELISA IH1 IH2	S	Psuedovirus VNT	34
Juno et al	Australia	Cohort	unstated	Convalescent	M	ELISA IH1 IH2	S RBD	Microneutralisation	41
Wang et al	China	Cohort	H	Inpatient	M/S	ELISA IH1 IH2 IH3 IH4 IH5	S1 S2 N RBD S	Pseudovirus VNT	23
Zeng et al	USA	Cohort	H	Inpatient	M/M	Epitope diagnostics	N	PseudovirusVNT	55
Ko et al	South Korea	Cohort	H	Inpatient	A	PCL	N, S	Microneutralisation	15
Ruetalo et al	Germany	Case series	PD	Community	A/M	Euroimmun Mediagnost Roche	S1 RBD N	VNT	49
Lee et al	USA	Cohort	PD	Convalescent	A/Md/Md/S	ELISA IH	RBD	PRNT	149
Wu et al	China	Case series	H	Inpatient	M	ELISA IH1 IH2 IH3	RBD S1 S2	Pseudovirus VNT	175
Bosnjak et al	Germany	Cohort	H	Inpatient	M	Euroimmun	S1	Surrogate VNT	40
Jaaskelainen et al	Finland	Case series	PD	Convalescent	M/Md/S	Euroimm Diasorin Abbott	S1 S1, S2 n/a	Microneutralisation	70
Percivalle et al	Italy	Cohort	PD	Convalescent	A/M/Md/S	n/a	n/a	Microneutralisation	38
Suthar et al	USA	Case series	H	Inpatient	M/Md	ELISA IH	RBD	FRNT	44
Zettl et al	Germany	Cohort	H	Inpatient	M/Md/S	Euroimmun	S1	VNT	25

(*Continued*)

Table 1. (Continued)

Author	Country	Study design	Setting	Participants	Disease Severity*	IgG Assay*	Target	Neutralising Antibody method	Sample size
Salazar et al	USA	Cohort	PD	Convalescent	M/Md/S	ELISA IH	S	Microneutralisation	68
Klein et al	USA	Case series	PD	Convalescent	M/Md	Euroimmun ELISA IH1 IH2	S1 S RBD	Microneutralisation	126
Padoan et al	Italy	Cohort	H	Convalescent	M/Md/S	Abbott Roche DIESSE Ortho Clinical Dxs	N N Native antigen S	PRNT	52
Gozalbo et al	Spain	Case series	Hospital	Inpatient	Md/S	ELISA IH	RBD	Pseudovirus VNT	51
Mueller et al	Germany	Case series	Community	Community	M	Euroimmun Diasorin Abbott Roche	S1 S1, S2 N N	VNT	34

*A = asymptomatic, M = mild, Md = Moderate, S = severe; IH = in house; hospital = H, Community = C, Plasma donor = PD; Bold = ELISA individual data extracted

reported at all titre cut-offs (Table 2). The pooled proportion positive varied with disease severity (Fig 3). Studies focusing on severe COVID-19 reported higher proportions with neutralising antibodies than studies focusing on mild COVID-19, especially if they had used titre thresholds >1:80 (84.8% [95%CI 80.0 to 89.2] and 56.7% [95%CI 49.9 to 62.9], for severe and mild COVID-19, respectively) or >1:160 (74.4% [95%CI 67.5 to 79.7] and 44.1% [95%CI 37.3 to 50.6], respectively). Similarly, the proportion of patients testing positive was lower in studies
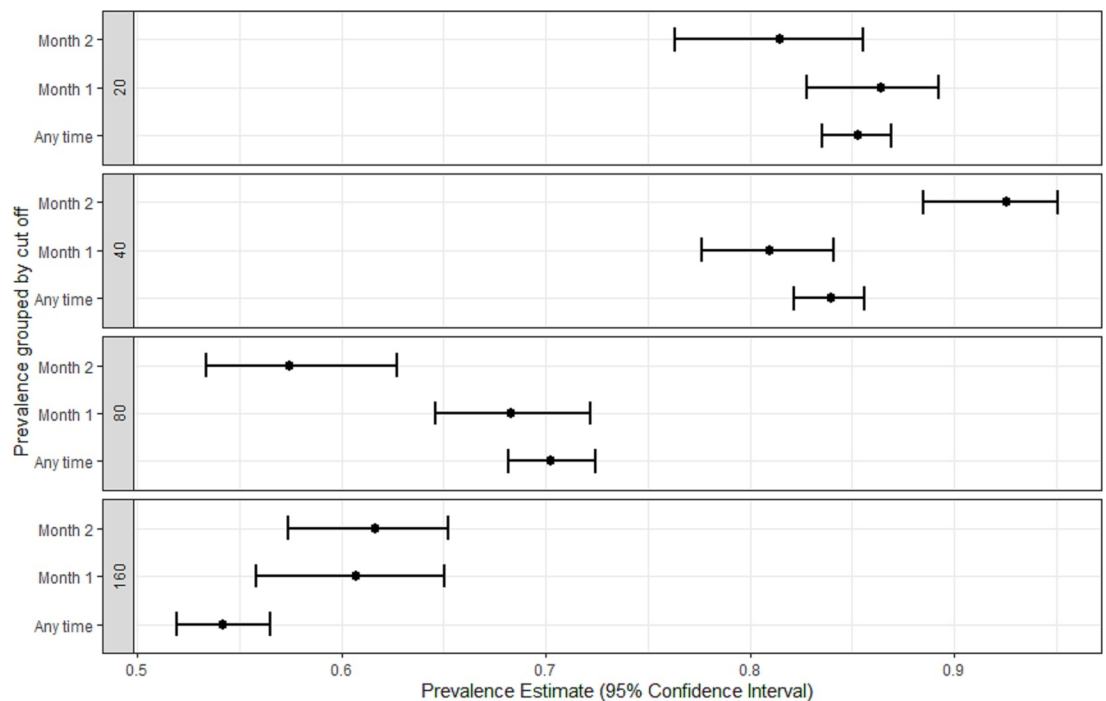

Fig 2. Estimated pooled proportion (95% confidence interval) of participants with neutralisation antibodies by titre cut-off and time.

Table 2. Estimated proportion of participants with neutralising antibodies with titre cut off > 1:20, 1:40, 1:80 and 1:160 by timepoints and selected covariates.

Variables	Cut off >20 % (95% CI)	Cut off >40 % (95% CI)	Cut off >80 % (95% CI)	Cut off >160 % (95% CI)
Any time				
Overall	**85.3 (83.5–86.9)**	**83.9 (82.2–85.6)**	**70.2 (68.1–72.5)**	**54.2 (52.0–56.5)**
Severity				
Asymptomatic	14.4 (2.3–35.4)	97.9 (89.1–100.0)	28.6 (17.9–39.2)	10.0 (3.7–20.1)
Mild	81.2 (76.5–85.3)	79.3 (74.2–84.2)	56.7 (49.9–62.9)	44.1 (37.3–50.6)
Mixed–excluding severe	93.2 (85.1–97.9)	87.1 (76.1–94.5)	68.9 (59.6–77.9)	53.1 (40.7–64.9)
Mixed–including severe	92.8 (88.6–96.2)	76.8 (72.9–80.2)	88.0 (84.3–91.2)	62.6 (57.7–68.5)
Moderate	82.3 (70.5–90.7)	86.1 (79.5–91.1)	73.6 (62.1–82.4)	57.6 (47.1–67.4)
Severe	89.3 (83.7–93.6)	90.0 (85.0–94.0)	84.8 (80.0–89.2)	74.4 (67.5–79.7)
Unknown	76.4 (57.0–90.1)	–	–	–
Setting				
Community	63.4 (57.6–70.0)	85.7 (80.6–89.9)	53.5 (46.6–60.2)	45.5 (39.9–52.4)
Plasma donor	78.9 (75.3–82.1)	66.8 (62.5–71.4)	66.0 (61.8–70.1)	41.1 (36.8–46.3)
Hospital	93.4 (91.0–95.1)	88.9 (86.7–90.9)	75.1 (72.7–78.2)	61.9 (58.9–64.8)
Hospital/Community	93.6 (86.9–98.2)	–	–	65.4 (57.8–89.6)
Not stated	–	98.3 (91.9–100.0)	–	–
Method				
VNT	76.8 (72.4–80.6)	81.3 (76.1–85.7)	54.3 (49.3–58.7)	43.4 (37.8–48.7)
Surrogate VNT	96.0 (90.8–98.7)	–	–	–
Microneutralisation	74.6 (69.5–79.1)	72.3 (68.6–75.8)	53.9 (49.4–58.3)	31.5 (27.4–35.8)
FRNT	95.1 (92.1–97.4)	95.5 (91.5–98.1)	88.4 (80.1–94.2)	79.0 (72.3–84.8)
PRNT	82.6 (77.2–87.6)	86.2 (82.8–90.3)	74.7 (69.6–82.9)	59.1 (54.2–65.5)
Pseudovirus	95.0 (91.0–97.5)	95.0 (91.6–97.3)	86.1 (82.7–89.0)	43.4 (37.8–48.5)
Month 1				
Overall	**86.4 (82.8–89.2)**	**80.9 (77.6–84.1)**	**68.3 (64.6–72.2)**	**60.7 (55.8–65.1)**
Severity				
Asymptomatic	–	–	–	–
Mild	77.3 (67.7–86.0)	70.7 (60.7–80.3)	54.1 (40.4–65.3)	50.3 (38.4–61.6)
Mixed–excluding severe	90.8 (77.7–98.0)	87.5 (62.2–99.4)	66.3 (35.1–90.7)	65.5 (33.9–89.3)
Mixed–including severe	93.7 (88.9–97.4)	88.0 (79.1–95.0)	72.6 (62.0–81.2)	61.6 (53.9–74.2)
Moderate	80.5 (70.7–90.2)	74.1 (65.0–83.5)	67.3 (58.2–77.2)	58.1 (50.7–66.8)
Severe	81.9 (65.6–90.2)	79.0 (69.6–87.2)	70.5 (62.1–79.1)	65.0 (46.8–74.6)
Unknown	–	–	–	–
Setting				
Community	98.3 (92.9–100)	98.8 (93.4–100.0)	97.7 (90.2–100.0)	97.6 (90.1–100.0)
Plasma donor	66.9 (55.0–75.2)	53.8 (45.2–61.8)	33.9 (26.1–42.4)	39.1 (29.7–46.6)
Hospital	92.5 (89.1–95.1)	90.0 (86.0–93.3)	77.8 (72.5–82.4)	70.6 (64.2–76.3)
Hospital/Community	93.8 (87.8–97.9)	–	–	–
Method				
VNT	–	–	54.1 (40.2–69.4)	–
Surrogate VNT	–	–	–	–
Microneutralisation	66.8 (55.0–75.2)	53.8 (45.2–61.8)	33.9 (26.1–42.4)	32.7 (20.5–41.4)
FRNT	94.0 (90.7–96.7)	93.4 (88.5–96.8)	81.0 (72.5–87.7)	68.6 (59.8–76.2)
PRNT	84.6 (75.3–92.2)	84.6 (75.1–91.9)	78.5 (68.5–87.3)	65.6 (58.3–76.7)
Pseudovirus	94.9 (90.2–98.0)	92.0 (86.0–96.5)	84.8 (77.5–90.6)	80.4 (71.6–87.7)
Month 2				

(Continued)

Table 2. (Continued)

| Variables	Cut off >20 % (95% CI)	Cut off >40 % (95% CI)	Cut off >80 % (95% CI)	Cut off >160 % (95% CI)
Overall	**81.5 (76.3–85.6)**	**92.6 (88.5–95.1)**	**57.5 (53.4–62.7)**	**61.6 (57.4–65.2)**
Severity				
Asymptomatic	–	–	19.0 (4.4–41.7)	6.9 (0.3–22.5)
Mild	66.2 (53.5–78.5)	87.7 (81.1 to 93.3)	48.4 (39.1–57.9)	25.8 (18.1–34.8)
Mixed–excluding severe	97.3 (91.6–99.9)	97.9 (92.3 to 99.9)	91.8 (82.3–97.6)	75.4 (62.8–85.8)
Mixed–including severe	88.0 (70.6–95.4)	88.7 (73.0 to 94.6)	64.3 (60.3–68.1)	77.7 (71.0–83.5)
Moderate	74.0 (56.4–86.5)	92.6 (77.8 to 99.6)	85.6 (57.1–99.2)	48.9 (17.0–79.5)
Severe	75.3 (65.1–84.9)	96.7 (90.0 to 99.7)	75.4 (61.7–89.3)	77.2 (64.6–88.3)
Unknown	–	–	–	–
Setting				
Community	–	–	–	–
Plasma donor	71.8 (64.1–78.8)	87.2 (77.6–93.7)	56.0 (49.2–60.8)	70.4 (61.9–77.7)
Hospital	87.3 (80.4–91.9)	91.8 (85.7–94.8)	57.9 (52.8–64.7)	58.7 (53.6–62.9)
Hospital/Community	–	–	–	–
Not stated	–	98.5 (93.2–100.0)	–	–
Method				
VNT	–	–	4.5 (0.6–12.1)	–
Surrogate VNT	–	–	–	–
Microneutralisation	71.8 (64.1–78.8)	93.7 (88.6–96.9)	52.8 (47.3–57.9)	37.3 (30.0–44.2)
FRNT	77.3 (54.8–90.9)	94.7 (75.9–100.0)	40.0 (28.1–52.0)	80.7 (60.3–93.0)
PRNT	86.3 (78.1–92.6)	73.3 (64.2–81.7)	64.5 (59.4–69.6)	71.6 (66.4–76.8)
Pseudovirus	93.7 (90.0–96.9)	97.5 (93.8–99.3)	79.5 (70.0–95.3)	73.9 (68.9–8.3)
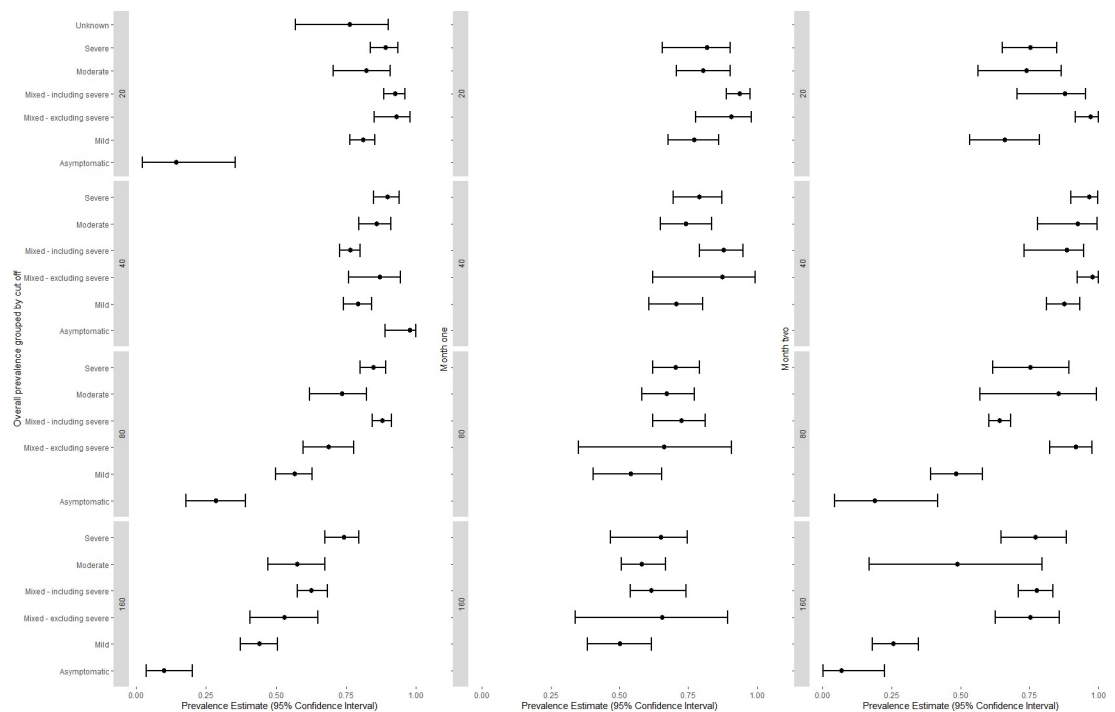
Fig 3. Estimated proportion positive (95% confidence interval) by disease severity, titre cut-off and time.

of asymptomatic infections (14.4% with a titre threshold >1:20 [95%CI 2.3 to 35.4]; 97.1% with a titre >1:40 [one study, 95%CI 89.1 to 100], 28.6% with >1:80 [95%CI 17.9 to 39.2] and 10.0% [3.7 to 20.1] with >1:160). These associations were reflected in studies recruiting patients in hospitals, which had higher proportions of participants with neutralising antibodies than those recruiting among plasma donors or the community (titres >1:20: 93.4% [95%CI 91.0 to 95.1] compared with 78.9% [95%CI 75.3 to 82.1] and 63.4% [95%CI 57.6 to 70.0], respectively).

Studies reporting the proportion of patients with neutralising antibodies one and two months after infection were analysed separately to assess the effect of time on the development of antibias during the early stages after infection. The pooled proportion with neutralising antibodies among plasma donors was higher in month two than in month one although this was not statistically significant for most thresholds (Table 2). In contrast, in studies recruiting from hospital settings, the proportion of participants with neutralising antibodies was higher in month two at titres > 1:80 (77.8% [95%CI 72.5 to 82.4] to 57.9% [95% CI 52.8 to 64.7], >1:160 70.6% [95%CI 64.2 to 76.3] to 58.7% [95%CI 53.6 to62.9]). The pooled prevalence one and two months after infection had the same overall pattern, with the proportions being higher among participants with severe than mild COVID-19 (Table 2). The proportion positive in month two was lowest with the microneutralisation method than with the FRNT, PRNT and pseudovirus methods at titres >1:160 (37.3% [95%CI 30.0 to 44.2]; 80.7% [95%CI 60.3 to 93.0], 71.6% [95%CI 66.4 to 76.8] and 73.9% [95%CI 68.9 to 78.3], respectively).

Correlation of neutralising and IgG antibodies

The modelled correlation between the aggregate proportion of patients with measurable IgG against SARS-CoV-2 and neutralising antibodies was very low (0.055, corresponding to poor correlation). The estimate was not modified by the assays, titre cut-offs used or the study setting (Table 3). The correlation between individual IgG and neutralising antibodies ranged from 0.16 to 0.756 across the studies (Table 4 and Fig 4). The correlation between individual values was higher than the correlation of aggregated data, but there was a high variability across studies, as shown in Fig 5. We were unable to explore whether the IgG ELISA or neutralising method used modified the correlations as each study used a unique set of IgG and

Table 3. Maximum likelihood estimates (95% confidence interval) of the bivariate binomial mixed model. The estimates for the intercept, titre cut off, setting and method are reported on the log-odds scale.

Covariate	Immunoglobulin G	Neutralizing antibodies
Intercept	5.398 (0.502 to 7.726)	2.903 (0.206 to 5.112)
Titre cut off	0.003 (-0.002 to 0.029)	-0.003 (-0.008 to 0.003)
Setting (ref. "Community")		
Hospital	-1.640 (-4.051 to 0.122)	-0.298 (-1.874 to 1.305)
Not stated	18.936 (0.334 to 56.965)	1.401 (-0.957 to 4.611)
Plasma donor	-1.658 (-3.996 to 0.137)	-1.163 (-2.994 to 0.574)
Method for nAB (ref. "FRNT")		
Microneutralisation	-0.504 (-2.220 to 1.230)	
PRNT	-0.782 (-2.436 to 0.757)	
Pseudovirus	0.639 (-2.176 to 0.820)	
VNT	-0.472 (-2.256 to 1.373)	
Random effects		
Variance	3.762 (0.217 to 5.001)	
Correlation	0.055 (4.793×10^{-9} to 0.500)	

Table 4. Maximum likelihood estimates of the correlation of IgG and neutralising antibody titres (nAB). Estimates reported in a log-odds scale with 95% confidence intervals.

Study	Correlation Estimate (95% Confidence intervals)
Ruetalo et al	0.727 (0.561 to 0.848)
Kohmor et al	0.589 (0.383 to 0.768)
Zettl et al	0.16 (0.01 to 0.776)
Severity (Baseline = Mixed without severe)	IgG: Severe 1.094 (0.491 to 1.697)
	nAB: Severe 2.363 (1.66 to 3.066)
Suthar et al	0.756 (0.589 to 0.87)
Jaaskaleinen et al	0.375 (0.155 to 0.662)
Severity (Baseline = Mild)	IgG: Moderate -0.669 (-1.55 to 0.211)
	IgG: Severe -0.608 (-1.545 to 0.33)
	nAB: Moderate -0.897 (-1.772 to -0.022)
	nABs: Severe -0.693 (-1.625 to 0.239)
Zhang et al	0.652 (0.503 to 0.776)
Severity (Baseline = Mixed without severe)	IgG: Severe 0·973 (0.321 to 1.626) nAB: Severe 1.141 (0.611 to 1.67)
Salazar et al	0.51 (0.356 to 0.661)
Severity (Baseline = Mild)	IgG: Severe 1.549 (0.919 to 2.179)
	nAB: Severe 1.401 (0.676 to 2.127)
Mueller et al	0.723 (0.53 to 0.858)
Severity (Baseline = Asymptomatic)	IgG: Mild 1.023 (0.275 to 1.771)
	nAB: Mild 2.543 (1.232 to 3.853)
Wang et al	0.597 (0.431 to 0.743)
Severity (Baseline = Mild)	IgG: Severe 0.564 (0.12 to 1.008)
	nAB: Severe 1.067 (0.614 to 1.521)

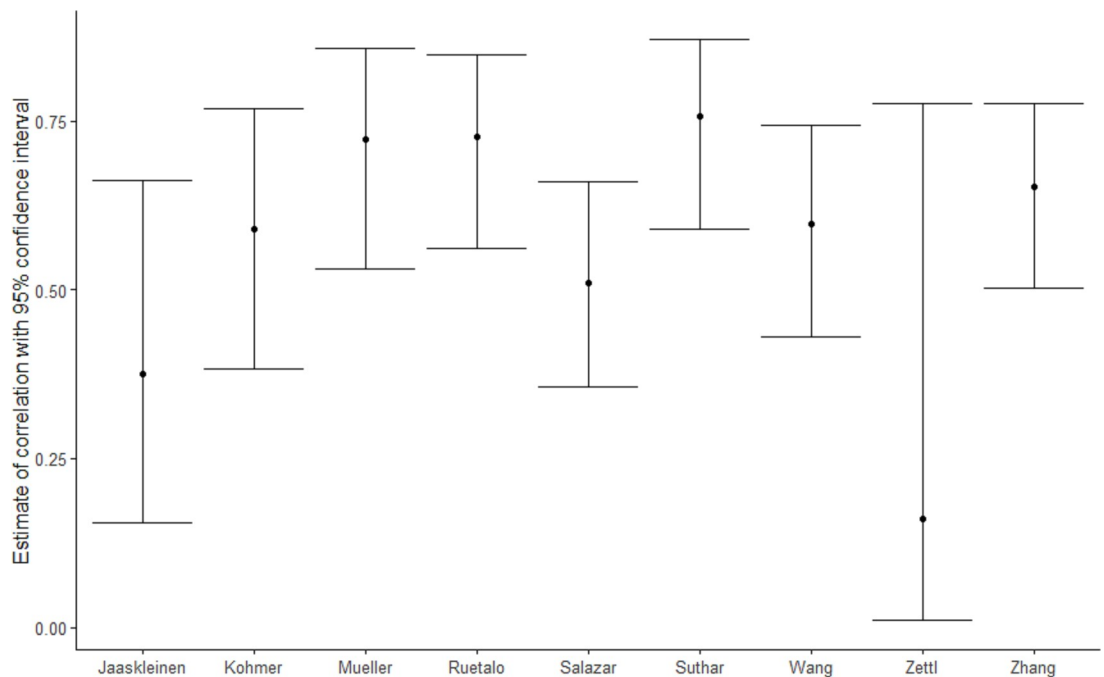IgG: immunoglobulin G. nABs: neutralising antibodies.

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Fig 4. Estimated correlation (95% confidence interval) of individual IgG and neutralising antibodies by study.

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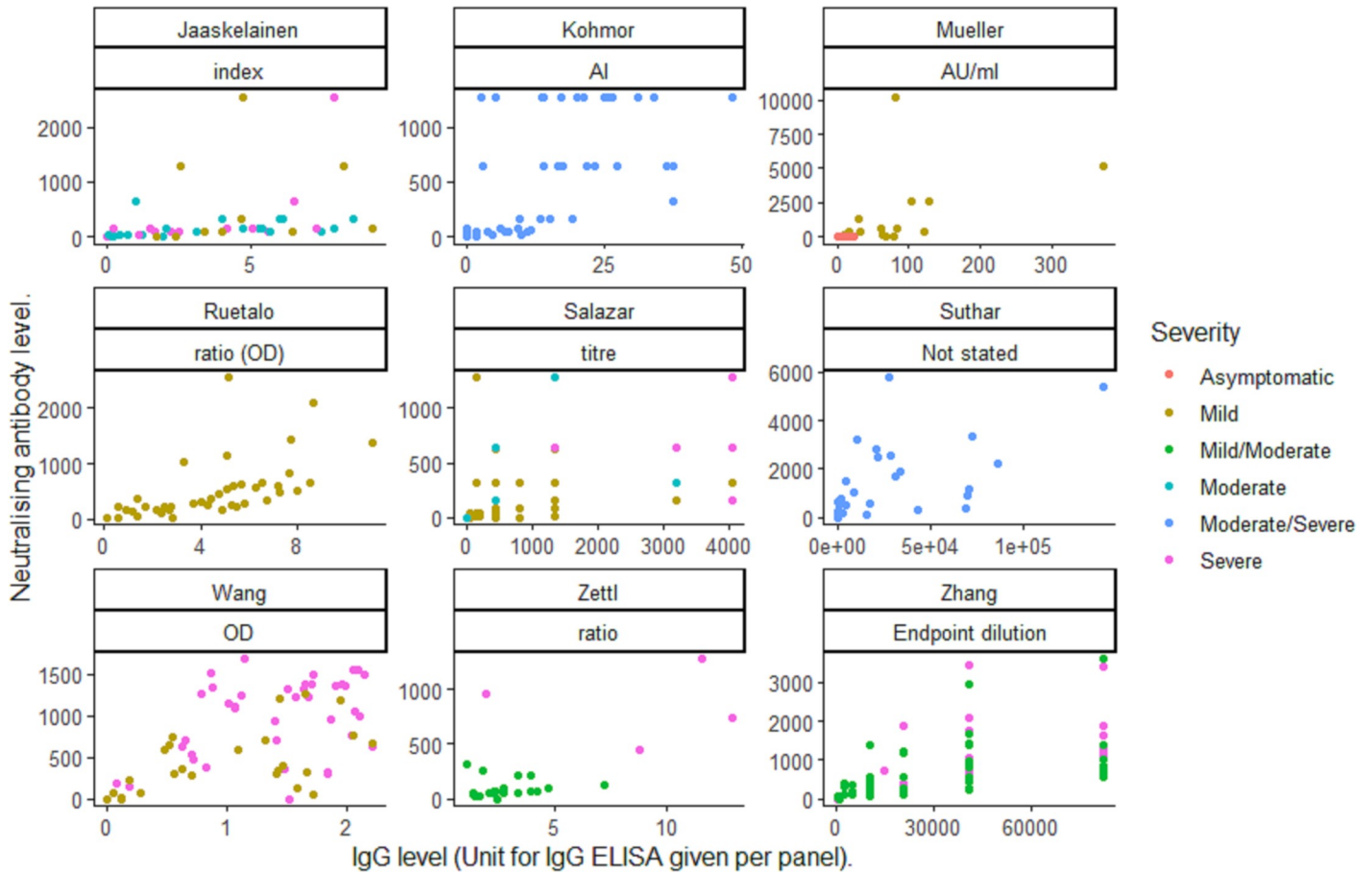
Fig 5. Scatterplot of individual neutralising and IgG antibody values by study.

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neutralisation methods. In five of six studies reporting disease severity [9–11,19,21,25], there was an increased correlation between IgG and neutralising antibodies with increasing disease severity [10,11,19,21,25].

Discussion

Despite major efforts to understand the mechanisms for immunity after COVID-19, this is the first comprehensive systematic review synthesising the proportion of individuals who exhibit neutralising antibodies after natural SARS-CoV-2 infection. Although 85% of participants with previous SARS-CoV-2 infection had detectable neutralising antibodies, there was a wide variation across studies, which was partly explained by the method and cut off titres used. Studies using the microneutralisation and the pseudovirus methods reported the lowest and highest proportion of participants with neutralising antibodies, respectively, while studies using low titre cut offs (i.e., >1:20 and >1:40) reported a higher proportion of participants as having neutralising antibodies than those using higher titre cut offs (i.e., >1:80 and >1:160).

The proportion of participants with neutralising antibodies varied with study setting, COVID-19 severity, and time since infection. Studies on severe COVID-19 reported higher proportions of patients with neutralising antibodies than studies focusing on mild and moderate COVID-19, with studies on asymptomatic infections having the lowest proportion of patients with antibodies. Similarly, hospital-based studies reported higher proportions of

participants with neutralising antibodies than studies based in the community or plasma donors, suggesting the study setting is a surrogate marker for disease severity. The lack of neutralising antibodies in a small but significant group of patients seen in this review might be explained by some patients having responses confined to SARS-CoV-2 antigens not identified by the assays used, or mediated through T cells, which are not detected by the neutralisation assays in this meta-analysis. Mild infections may also elicit responses that are restricted to the mucosal cells, where defence responses are dominated by the secretory immune system [36].

Only a subset of studies reported the pooled proportion of neutralising antibodies one and two months after infection. The proportion of participants with neutralising antibodies in the second month was slightly higher among plasma donors and slightly lower among patients recruited from hospital. However, the differences were small and confidence intervals overlapped. As neutralising antibodies peak within 21 days after symptoms onset, and symptoms onset if often poorly documented, it may be that the one-month timepoint is not ideal to demonstrate differences over time [37].

Surprisingly, the correlation between the detection of IgG and neutralising antibodies at study level was low, with a better correlation for the subset of studies with individual data. This is not surprising, as the correlation of aggregate data is necessarily a less sensitive analysis than individual data that can show higher definition. The correlation of individual IgG levels increased with disease severity, reaching an r value of 0.756, but with a high variation between studies. This lack of consistency can be attributed to the neutralisation and ELISA assays used. Neutralisation assay sensitivity varies across the methods and ELISAs are based on different SARS-CoV-2 antigens (*e.g.* nucleoprotein or spike protein domains), which affect performance [38].

Despite neutralising antibodies not being detectable in a significant proportion of participants, these antibodies are only a visible fraction of the defence mechanism against COVID-19 and second infections are rare and adaptive immunity mechanisms involving B and T cells and mucosal neutralising antibodies are at play [39]. For example, memory B cells display clonal turnover after six months, with maturation of response and expressed antibodies having greater somatic hypermutation, increased potency, and resistance to the Spike protein receptor-binding domain mutations, indicative of a continued evolution of the humoral response [39].

We have examined variations resulting from study settings, testing methodologies, and disease severity and provide an overview based on a large number of studies, resourcing to individual data whenever possible. We have shown that current information is based on a multitude of methods assessing neutralising antibodies, a large variety of ELISAs, including in-house methods without WHO endorsement, and that these differences lead to different proportions of individuals being classified as having positive responses and, possibly, the poor correlation between IgG and neutralising antibodies in aggregated datasets. These limitations highlight the need for standardisation of the methodology and the development of guidelines for future studies. There is a similar a lack of standardisation of objective markers on the assessment of disease severity (e.g., C Reactive Protein) and results are often presented without stratification, which made it difficult to perform meta-regression of subgroups. Moreover, data on circulating SARS-CoV-2 variants, patients' age, outcome, T cell responses, ELISA's spike glycoprotein targets, and other potential covariates were not available in significant numbers and there were no studies from South America, the Indian subcontinent, or Africa, and results cannot be generalised to these populations.

In the event of a new pandemic virus there is a limited window where the natural epidemiology of the virus can be observed prior to treatment or vaccination. Without large cohort studies only, a fragmented picture was available, and ongoing cohorts will need to account for

virus variants, treatment and vaccination. Combining studies and performing a meta-analysis allowed an analysis of data from early stages and gives a more complete picture of the natural immunity at the beginning of the pandemic.

In conclusion, a high proportion of individuals have evidence of neutralising antibodies after SARS-CoV-2 infection. These proportions vary with disease severity, with asymptomatic infections being less likely to have detectable antibodies than those experiencing severe COVID-19. Most diagnostic tests, therapeutics, and vaccines are aimed at the SARS-CoV-2 Spike, and virus evasion occur through mutations that escape neutralising antibodies. Thus, research is needed to establish whether the lack of detectable neutralising antibodies interrelates with virus escapees with or without a vaccine [40]. This is particularly relevant in light of the recent dominance in parts of the UK of a strain with mutations in the spike protein that is associated with increased transmissibility [41]. Moreover, the minimum level of neutralising antibodies required to achieve protection is unknown at this stage, and immunological memory mechanisms may rapidly boost generation of antibodies that are not detectable in the peripheral blood in the absence of stimulation. This review also highlights the need for guidance on standardised protocols for the measurement of neutralising antibodies; for longitudinal studies to document how neutralising antibodies and their relationship with IgG levels change over time, and whether minimal or undetectable levels indicate lack of clinical protection and thus vulnerability to infection.

Supporting information

S1 Table. Full search strategy.
(DOCX)

S2 Table. Risk of bias of the studies included using the Quality Assessment Tool for Cohort and Case Series Studies of the National Institutes of Health (NIH).
(DOCX)

S1 Text. Statistical analysis.
(DOCX)

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