

Prior COVID-19 protects against reinfection, even in the absence of detectable antibodies

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Abstract

We examined 49450 patient laboratory records, from four UK laboratories (three in London, and one in Newcastle-upon-Tyne), for evidence of SARS-CoV-2 infection in the first wave of the COVID-19 Pandemic (March – May 2020), evidence of an antibody response, and evidence of infection or reinfection in the second wave (August 2020 – January 2021).

We identified 224 RNA-positive antibody-negative patients in the first wave, of whom two had a laboratory-confirmed reinfection in the second wave (0.89%), compared to 2054 infections in the 47139 patients with negative serology and either no RNA result, or a negative RNA result (4.36%), implying a relative risk of 0.20 (95% CI 0.05 to 0.81). We also found 2087 RNA-positive antibody-positive patients in the first wave, with 18 reinfections (0.86%) – this was similar to the rate in the RNA-positive antibody-negative patients (relative risk 1.04).

These results suggest that the absence of a measurable antibody response to SARS-CoV-2 infection does not imply a lack of protective immunity. Possible mechanisms include mucosal antibody responses, memory B cells, T-cell-mediated immunity, or serum antibodies not detectable by routine laboratory assays. This highlights the complexity of the immune response, and possible limitations of using simple antibody assays for tests of population and individual immunity.

Introduction

Several studies, including from our own centres, have shown the strong protection from reinfection conferred by previous SARS-CoV-2 infection (1-5) However these studies did not address whether prior infection is protective in the absence of a detectable humoral immune response. Patients with primary or secondary antibody deficiency syndrome and reduced or absent B cells can recover from COVID-19 (6,7). Although there have been few mechanistic studies, preliminary data show that such individuals generate striking T-cell immune responses against SARS-CoV-2 peptide pools (8). SARS-CoV-2 specific T cell immune responses but not neutralising antibodies are associated with reduced disease severity suggesting the immune system may have considerable redundancy or compensation following COVID-19 (9). It is plausible that mucosal immunity, memory B-cells, or other classes of antibody may also play a significant role in protection, although direct evidence is lacking (10).

Methods

We examined datasets from four UK laboratories and identified a subset of patients with proven SARS-CoV-2 infection, defined as laboratory detection of RNA, in the first wave of the pandemic between March and May 2020, but with negative serology results in June and July. SARS-CoV-2 RNA test results (PCR or other nucleic acid amplification technology) between August 2020 and January 2021 were reviewed to identify patients with likely reinfection in the second wave of the UK pandemic. Repeat positive results within 90 days were discounted. A comparator group of patients with no evidence of infection in the first wave – *i.e.* negative serology with either a negative or no RNA assay performed - was used to calculate the relative risk of infection in those with and without prior infection. A second comparator group was also examined, who were RNA-positive and antibody-positive in the first wave. A significant proportion of the patients were healthcare workers, who were offered serology as part of a national policy. We terminated the study at the end of January, as we judged that the national vaccination rollout might interfere with the reliability of results thereafter.

Results

The results are summarised in the Table. We identified 224 RNA-positive antibody-negative patients in the first wave, with two laboratory-confirmed reinfections in the second wave (0.89%), compared to 2054 infections in the 47139 patients with negative serology and either no RNA result, or a negative RNA result (4.36%.) This implies a significantly reduced risk of reinfection (relative risk 0.20, 95% CI 0.05 to 0.81) in those with prior SARS-CoV-2 infection but without detectable antibodies, compared to those with no previous evidence of infection. We also found 2087 RNA-positive antibody positive in the first wave, with 18 reinfections (0.86%) – this was similar to the rate in the RNA-positive antibody-negative patients (relative risk 1.04).

Discussion and Conclusions

Our results indicate that antibodies (as detected by routine laboratory assays) are not essential for protection against reinfection. To our knowledge this is a novel observation, though it is supported by a recent report that immunity to SARS-CoV-2 in patients without antibodies can occur if there is a significant T cell immune response (8). IgG memory B cells against SARS-CoV-2 increase and exhibit greater affinity maturation over time despite a decline in serum antibody titres (11,12). This is consistent with the known development of the immune response: the loss of antibody may reflect not so much waning immunity but rather standard contraction of immune responses following SARS-CoV-2 infection, with development of antigen specific memory B cells. In addition, mucosal IgA or IgG may explain some of the protective effect we have observed. Furthermore, given the long incubation and slow onset of severe

disease in SARS-CoV-2 infection, it is biologically plausible that the 2-3 day response time of antigen specific memory T- or B-cells is sufficient to protect against reinfection independently of circulating antibody, as is seen with Hepatitis B vaccination (13)

The principal limitation of this study is that it is a retrospective pragmatic review of pooled clinical laboratory datasets. As such, SARS-CoV-2 RNA testing in many individuals will have been event-driven, rather than routine screening, and some cases of SARS-CoV-2 infection may have been missed, for example if asymptomatic. Furthermore, the criteria for seropositivity were set by the assay manufacturers; it is possible that some patients had specific antibody below the limit of assay detection, that nonetheless contributed to protection. Due to the deployment of different assays across laboratories, we were unable to examine the relationship between antibody index and risk of reinfection. The comparator group, of necessity, may have included some patients who also had antibody-negative infection in the first wave but who did not have an RNA assay performed. However, any such missed cases would have tended to reduce the apparent difference between the two groups, which increases confidence in our findings. We cannot exclude the possibility that positive test results may have influenced individual behaviour, potentially increasing the risk of (re)infection or making seropositive individuals reluctant to come forward for further testing if they developed COVID-19 symptoms. However a recent Danish study showed no difference in protection from reinfection in health care workers tested regularly for SARS-CoV-2 infection, compared to other population groups (4). Finally, given the evolving epidemiology of the SARS-CoV-2 Pandemic, and the continual emergence of new strains, we can only say with confidence that our results apply to the situation in the UK up to the end of January 2021.

In conclusion, our results add to the emerging evidence that detectable serum antibody may be an incomplete marker of protection against reinfection. This could have implications for public health and policy-making, for example if using seroprevalence data to assess population immunity, or if serum antibody levels were to be taken as official evidence of immunity – a minority of truly immune patients have no detectable antibody and could be disadvantaged as a result. Our findings highlight the need for further studies of immune correlates of protection from infection with SARS-CoV-2, which may in turn enhance development of effective vaccines and treatments. Serum antibody, whilst convenient to measure, is but a small window on the complex world of the human immune system.

Table:

Numbers of patients and SARS-CoV-2 (re)infections identified in the participating laboratory datasets.

		SWLP	NWLP	NCLE	KCH	Total	Significance; 95% confidence intervals
Test group: Confirmed infection, serology negative in first wave	RNA-positive, Antibody negative in first wave	98	75	28	23	224	
	Reinfected in second wave	1	1	0	0	2	
	Proportion reinfected	1.02%	1.33%	0%	0%	0.89%	
Comparator Group 1: No laboratory evidence of infection in first wave	RNA negative or not tested; Antibody negative in first wave	23289	6389	10138	7323	47139	
	Infected in second wave	639	562	443	410	2054	
	Proportion infected	2.74%	8.80%	4.37%	5.60%	4.36%	
	Relative risk	0.37	0.15	0	0	0.20	p = 0.02; CI = 0.05 to 0.81
Comparator Group 2: Confirmed infection, serology positive in first wave	RNA positive, Antibody positive in first wave	852	311	380	544	2087	
	Reinfected in second wave	5	8	0	5	18	
	Proportion reinfected	0.59%	2.57%	0%	0.92%	0.86%	
	Relative risk	1.74	0.52	*	0	1.04	p = 0.96; CI = 0.24 to 4.43

SWLP: South West London Pathology

NWLP: North West London Pathology

NCLE: Newcastle-upon-Tyne Laboratories

KCH: King's College Hospital Laboratory

* Relative risk undefined (0/0)

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