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Update note on immunity to SARS-CoV-2 after natural infection

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Summary

1. Most people infected with SARS-CoV-2 generate an antibody response in serum, saliva and mucosal fluids within 1–3 weeks after symptom onset. However, there is heterogeneity, some with mild disease developing weak antibody responses.

2. Antibody is detectable in saliva for at least 8 months, and in blood for at least 9 months after infection (high confidence) but individual trajectories vary and levels depend on the assay method (of which there are many).

3. Cells making antibody (plasma cells) or with the capacity to rapidly make antibody (memory B cells) can be detected up to 8 months after infection.

4. Most convalescent individuals show T cell responses to SARS-CoV-2 after infection, that can be detected for at least 8 months. However, activated virus-specific T cells are only transiently present in the peripheral circulation at measurable levels and thereafter need to be recovered by restimulation *in vitro*. T cells have antiviral effects on contact with infected cells, but not when circulating free in the blood.

5. Memory B cells and specific T cells enhance long-term protection against severe COVID-19 caused by current and (to a lesser extent) future variants of SARS-CoV-2.

6. These immune responses lessen disease severity (high confidence) but may also reduce viral replication in the respiratory mucosa and inhibit SARS-CoV-2 transmission (moderate confidence).

7. Following natural infection with SARS-CoV-2:

    a. Protection against symptomatic PCR-confirmed infection with SARS-CoV-2 is high for a period of at least 7 months, estimated at 81% (95% CI 75-84%) (high confidence).

b. Protection against all PCR-confirmed infections with SARS-CoV-2 is high for a period of at least 6 months, estimated to be 69% (95%CI – 60-76%) (high confidence).

c. Protection against asymptomatic or atypical PCR-confirmed infections with SARS-CoV-2 is moderate for a period of at least 6 months, estimated at 40% (95% CI 20-55%) (high confidence).

d. Protective effectiveness against symptomatic PCR-confirmed infection in those aged over 65 is lower than in younger age groups, estimated at 47.1% (95%CI 24.7-62.8%) (low confidence).

8. Protection against SARS-CoV-2 infection, disease, and transmission may be diminished by antigenic changes in variant viruses (high confidence).

Background

9. Immunity generated following infection with SARS-CoV-2 may be:

    a. Sterilising: providing protection against both infection and illness

    b. Functional (disease limiting): protection against severe illness but not against infection;

    c. Ineffective: providing little protection against illness or infection;

    d. Disease-enhancing (a theoretical possibility, not yet observed).

10. Neutralising antibodies may lead to sterilising immunity and are currently a useful correlate of protection for both natural and vaccine-acquired immunity.

11. However, understanding natural immunity to SARS-CoV-2 requires consideration of a full range of immune responses.

12. Protection against SARS-CoV-2 infection may be mediated through multiple mechanisms including innate defences, mucosal antibodies, systemic antibodies, tissue-resident CD4+ and CD8+ T cells, memory T and B cells in lymphoid organs, and antibody-producing plasma cells.

13. This paper considers the immunology and durability of the humoral and cell-mediated responses that occur following natural SARS-CoV-2 infection. The immunology of the response to vaccination is summarised elsewhere.

Contribution and durability of the antibody response to SARS-CoV-2 infection

14. There is considerable heterogeneity in antibody responses to COVID-19, and responses are correlated with severity of infection [1, 2, 3, 4, 5, 6].

15. Within 2–4 weeks of symptom onset, most healthy young individuals infected with SARS-CoV-2 generate an antibody response in serum [2, 4, 7, 8] and saliva [9].

16. Nearly all convalescent sera, including those from people with asymptomatic infections, show neutralisation activity [10, 11, 1, 5].

17. Data from animal models show that neutralising antibodies can provide protection against COVID-19 [12]. In rhesus macaques, relatively low neutralising antibody titres can protect from reinfection with SARS-CoV-2, and lower 'sub-sterilising' titres still reduce disease severity and provide functional immunity [13, 14].

18. Epidemiological data show that antibodies are associated with protection from reinfection. Two large studies of healthcare workers showed that antibody responses provide protection from re-infection for up to 7 months of follow up [15, 16]. Investigations of outbreaks with high attack rates have shown that the presence of antibodies is associated with protection from disease and reinfection [17, 18].

19. The S (transmembrane spike) glycoprotein and N (nucleocapsid) protein are the main targets of antibody induced by SARS-CoV-2 infection. While antibody against the N protein do not neutralise, antibody against the S protein (specifically the receptor binding site [RBD] of the S1 subunit) correlates strongly with neutralising activity [2, 4, 10].

20. Antibody-mediated protection from SARS-CoV-2 may consist of more than neutralising activity: antibody Fc effector functions such as antibody-dependent complement deposition and antibody-dependent cellular cytotoxicity are documented for other respiratory viruses [19] and have been induced by experimental vaccination against SARS-Cov-2 [13, 14].

21. Neutralising antibody is associated with a reduction in shedding of infectious virus in hospitalised patients [20].

22. Reinfection with SARS-CoV-2 remains rare but may become frequent as immunity increases in the population and selective pressure drives the emergence of variants.

23. Antibody against Receptor Binding Domain (RBD) or Spike measured in serum or plasma is likely to correlate with protection against SARS-CoV-2 infection and COVID-19. The protective effect of naturally acquired baseline antibodies against PCR-confirmed infection with SARS-CoV-2 is described later in this paper.

24. Antibody-mediated neutralising activity is detectable in both blood and saliva up to 8 months following infection [21, 22, 3, 9, 10].

25. While SARS-CoV-2 specific IgM has been found to decline within a few months of acute infection [3] , IgG kinetics are more stable. Specific IgA in serum and saliva shows more rapid decay than IgG [9], but is maintained at low, yet stable, levels in the sera of some individuals [21, 8]. This implies that sterilising immunity may be shorter-lived than functional protection.

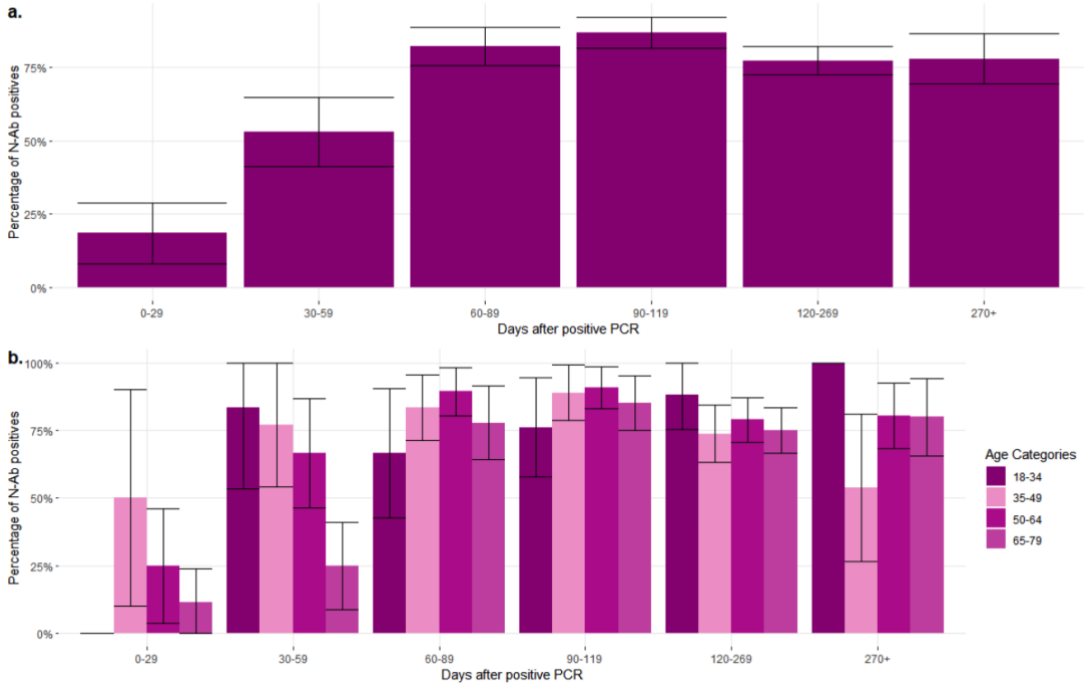
26. The Virus Watch Study described the trajectory of the Nucleocapsid antibody response to infection in 649 participants with a known date of testing positive for COVID-19 on nose/throat swabs. N-antibody response was measured using Roche quantitative assays on micro-capillary finger-prick samples, as this is not affected by vaccination (which stimulates production of antibodies to spike but not nucleocapsid).

    a. In all age groups antibodies to nucleocapsid rise following infection and remain markedly higher than at baseline for at least 9 months.

    b. Overall, antibody titres peak in the third month after infection and then begin to decline from the fourth month (p=0.009).

    c. The trajectory appears to depend on the age of the person infected. Antibodies remain at low levels in those aged over 65 until three months after infection. In those under 50, antibody appears to rise faster, peaking at two months and beginning to decline from three months after infection. In those over 50, antibody rises more slowly, peaking at three months and beginning to decline from four months after infection.

Figure 1 – N Antibody positivity amongst 649 samples with known date of infection



27. There is some heterogeneity in antibody responses to SARS-CoV-2 between individuals. Not all individuals who are infected will produce a robust antibody response. Antigen load (probably related to disease severity) affects initial antibody titres [7, 23]. Those with higher initial antibody levels usually have longer-lived protection and slower antibody decay rates [24]. In addition, rapid recovery from illness is associated with sustained antibody response in individuals with mild COVID-19 [25].

28. There is a report that those with mild or inapparent infection are at risk of developing 'Long COVID' (post-COVID syndrome, PCS) with symptoms of anosmia, ageusia, fatigue or shortness of breath month 4 and 7. In this study, lower baseline levels of SARS-CoV-2 IgG were associated with higher risk of developing long-term symptoms [26].

29. Natural infection with other respiratory viruses provides long-lived antibody-mediated protection. It is likely that antibody-mediated protection against SARS-CoV-2 would follow a similar pattern.

    a. For SARS-CoV-1, around 90% of individuals have neutralising antibody at 3 years post infection, and specific IgG has been detected in some individuals up to 13 years after infection [27].

    b. Following natural infection with influenza, neutralising antibodies are maintained for life, providing some immunity against homologous strains [28].

    c. Human experimental studies of common cold coronaviruses show that adult volunteers have antibody levels that remain high a year after infection, and correlate with total or partial immunity upon re-challenge with homologous virus [29, 30].

30. Increased viral transmissibility, such as that reported for the B.1.1.7 variant, could increase the titre of neutralising antibodies required for protection and thereby shorten the duration of effective immunity.

31. Recently, 'variants of concern' such as B.1.351 have been associated with reduced neutralisation by convalescent sera [31]. Viral evolution and the emergence of variants that show antigenic distance from previous types may lead to diminished antibody-mediated protection.

Protective effect of naturally acquired antibodies against SARS-CoV-2 infection

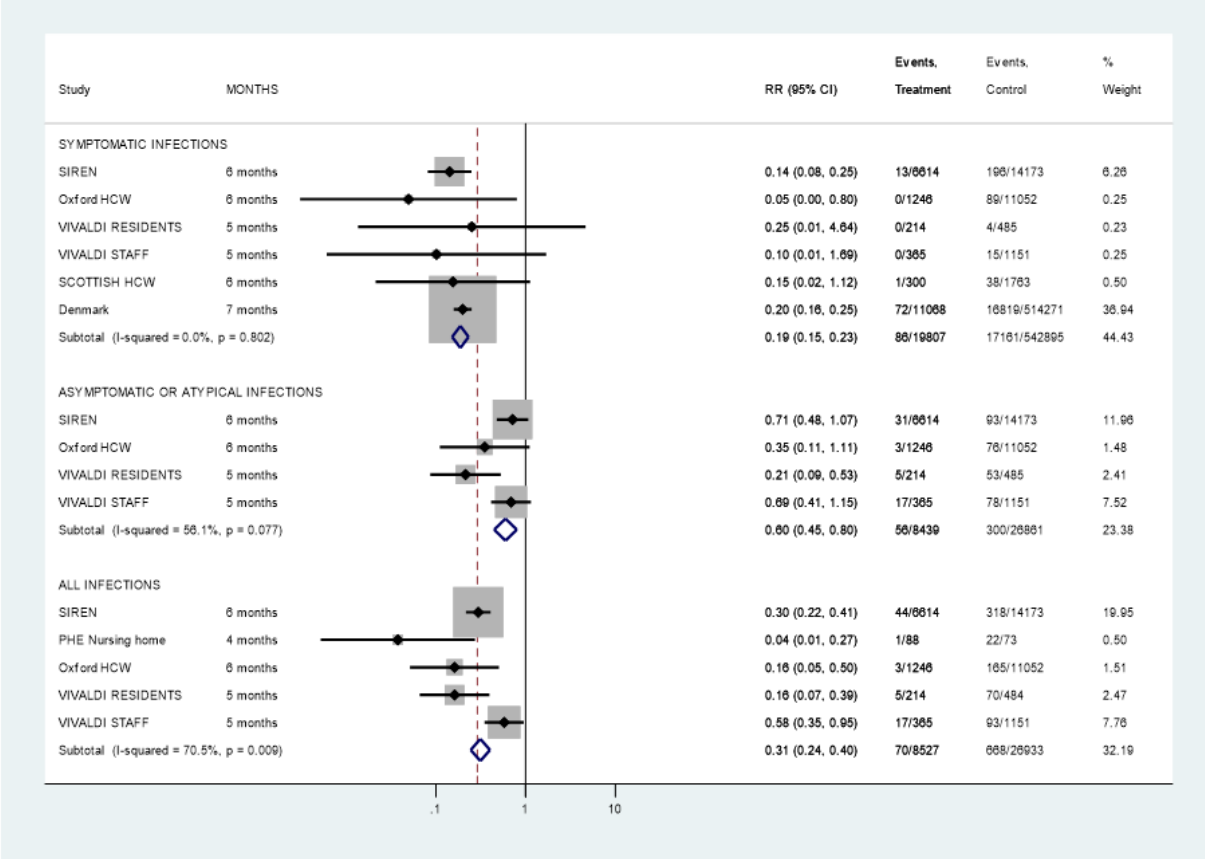
32. To understand the relationship between naturally acquired baseline antibodies and protection against PCR-confirmed infection, a meta-analysis of studies with more than three months of follow up and regular antigen testing after an antibody test was performed. A total of 6 studies are included. [32, 33, 16, 15, 34, 35]

33. One whole population study from Denmark which did not include antibody testing but followed up those who had previously tested PCR positive to COVID-19 was also included [35]. This study was able to assess protective effect of prior PCR confirmed disease against subsequent PCR confirmed infection and was based primarily on symptomatic swabbing as part of the national testing programme. It was also able to assess the protective effect in different age groups.

34. Where possible analyses were stratified by whether the infection was symptomatic (with typical COVID symptoms), asymptomatic or with symptoms that do not meet the COVID-19 case definition (of cough, fever or loss of or altered sense of smell or taste) and all infections combined.

35. The figure below shows the forest plot for the relative risks derived from these studies. These relative risks assume equivalent person follow up time in those with and without baseline antibodies.

Figure 2 – Meta-analysis of protective effectiveness of baseline antibodies against PCR confirmed infection



36. Protective effectiveness of baseline antibodies/prior infection against infection was calculated as 1-RR * 100.

37. The pooled estimate of the protective effectiveness of prior infection against subsequent symptomatic PCR confirmed infection was 81% (95% CI 75-84%). The large data linkage study of PCR confirmed infections in Denmark contributed most data to this – when this was excluded the protective effectiveness was 86% (95% CI 77%-92%).

38. The pooled estimate of the protective effectiveness against asymptomatic or atypical PCR confirmed infections was 40% (95% CI 20-55%).

39. The pooled estimate of protective effectiveness against all PCR confirmed infections (regardless of symptoms) was 69% (95% CI 60%-76%).

40. The largest of these studies was based on data linkage in Denmark and was able to examine protective effect of prior infection against symptomatic disease in different age groups. This found a substantially lower protective effectiveness in those aged >65 (47·1% (95% CI 24·7–62·8). There was no apparent drop off in protection against symptomatic infection comparing those with 3-6 months of follow up and those with 7-10 months follow up.

41. In conclusion, although baseline antibodies derived through natural infection provide strong protection against symptomatic infection over a period of at least 7-10 months, protection against asymptomatic infection is substantially less and protection appears to be lower in those aged > 65 years.

Contribution and durability of B cell response to SARS-CoV-2 infection

42. B cells are an important mediator of the antibody response to respiratory viruses.

43. During acute viral infection, naïve B cells undergo clonal expansion and produce short-lived plasmablasts and plasma cells that secrete mainly lower-affinity antibodies. Some activated B-cells differentiate into long-lived memory B cells and plasma cells which secrete higher-affinity antibodies (affinity maturation) and are responsible for maintaining protective levels of specific antibody once antigen is cleared [36, 37, 38].

    a. In one study, plasma cells specific to SARS-CoV-2 were present 8 months post-infection in most bone marrow donors [39]. Thus far, the reported kinetics of the S-specific IgG response in COVID-19 are consistent with long-term survival of plasma cells, suggesting that long-lived plasma cells are likely to persist far beyond the 8 months already shown [40, 21, 39].

44. Memory B cells direct the antibody recall response against viruses and can be sustained for life [28]. Upon re-exposure to antigen, memory B cells can rapidly differentiate into plasma cells or re-enter germinal centres to boost humoral immunity, and thus play a key role in sustaining antibody-mediated protection in the long term [41].

    a. S protein specific memory B cells appear as early as 2 weeks following SARS-CoV-2 infection but are very rare in unexposed individuals [40].

    b. SARS-CoV-2 specific memory B cells increase steadily in the months following infection and are still present up to 6 months after, suggesting that B cell memory to SARS-CoV-2 is likely long-lasting [21, 22].

    c. Compared with non-hospitalised cases, RBD-specific memory B cells are increased in hospitalised cases [21], indicating that antigen load is an important determinant of the strength of the humoral response.

45. In summary, robust B cell responses are mounted in response to SARS-CoV-2 infection in nearly all individuals and are sustained for at least 8 months.

Contribution and durability of T cell response to SARS-CoV-2 infection

46. T cells play an important role in the immune response to respiratory viruses.

47. Early T-cell responses during COVID-19 are associated with reduced disease severity and rapid viral clearance [42, 43].

48. Most convalescent individuals show robust circulating CD4+ and CD8+ memory T cell responses to SARS-CoV-2 regardless of the severity of their illness [44, 45, 46]. These are present for over 8 months after infection [21, 47].

49. Infections with many respiratory viruses are essentially confined to the respiratory tract. Memory T cells mostly reside in regional lymph nodes and have to undergo proliferation at that site before recruitment to mucosa via the circulation [48]. As this process takes 2–4 days and leads to a delay in the memory T-cell response to respiratory viral infection, circulating T cell-mediated immunity cannot achieve instantaneous 'sterilising' immunity [49]. However, there is a correlation between numbers of specific circulating CD4+ and CD8+ memory T cells and the severity of influenza infections in humans [50, 51].

50. It is possible that T cell responses are important where antibody responses are insufficient to provide protection. In rhesus macaques with low antibody titres, depletion of CD8+ cells prior to re-challenge partially abrogates protective immunity [13].

51. In comparison to neutralising antibodies that are directed to specific sites on viral surface glycoproteins, T cells recognise peptides from varied targets (including well conserved internal proteins). T cell responses may also be present in people who have recovered from mild SARS-CoV-2 infection, but who lack neutralising antibodies [52].

52. Following infection with SARS-CoV-2, Memory T cell populations are generated that are specific to non-structural, membrane, N, and S proteins [21]. Such T cells may be important if escape mutants are generated by the selective pressure of neutralising antibodies specific to S-protein.

53. Analysis of the T cell response to SARS-CoV-2 shows that nearly all individuals produce RBD-specific T cell clones, and that some regions are immunodominant, including the S346-365 region, which is well-conserved across SARS-CoV-2 variants [53].

54. The eventual duration of protection mediated by specific memory T cells against SARS-CoV-2 remains unknown. However, data from other viruses including RSV and SARS-CoV-1 suggest that circulating memory T cell responses to respiratory viruses can be very prolonged [54, 55, 46]. CD4+ and CD8+ memory T cell responses to SARS-CoV-1 are present at 11 and 17 years following infection in some individuals [46, 55].

55. Tissue-resident memory T cells can mount quick immune responses *in situ*, and their presence in the airway contributes to protection against SARS-CoV-1 and MERS-CoV [56].

56. Tissue-resident memory T cells also appear to play a role in protection from SARS-CoV-2; rhesus macaques depleted of CD8+ cells showing higher viral loads in the upper respiratory tract one day post infection, suggesting tissue resident memory T cell activity [13]. Currently, there are insufficient data to determine the duration of tissue-resident T cell populations in humans, though they have been observed to survive for over a year in the lung [57].

Conclusions

57. Infection with SARS-CoV-2 leads to antibody, B cell, and T cell responses in almost all individuals, which are sustained for over 8 months after infection (high confidence).

58. Virus-specific IgA and tissue-resident T cells provide mucosal protection against SARS-CoV-2 but may have limited duration (moderate confidence).

59. Neutralising antibodies to SARS-CoV-2 can lead to sterilising immunity, and measurement of antibodies against RBD or S1 using robust serological assays is likely to correlate with protection against natural exposure to SARS-CoV-2 (moderate confidence).

60. Data from other respiratory viruses suggest that a combination of neutralising antibodies produced by long-lived plasma cells, and immunological support from memory B and T cells, can provide long-term protection against severe disease (high confidence).

61. Data are insufficient to assess the impact of natural immunity on transmission, though the presence of neutralising antibody is associated with a reduction in shedding of infectious virus (moderate confidence).

62. Immunity against SARS-CoV-2 infection may be diminished by viral evolution and the emergence of variants (high confidence).

63. Disease attenuating (functional) immunity is more likely to be maintained long-term than sterilising immunity because lower levels of immunity are needed to attenuate severity as opposed to preventing infection (moderate confidence).

Recommendations

64. Studies with longer follow up post-infection are required to understand the duration of antibody, B cell, and T cell mediated immunity.

65. While antibodies to SARS-CoV-2 play an important role in protection from infection and disease, studies of innate mucosal defence and the B and T cell responses must also be prioritised.

66. Continued monitoring of immunity to new variants is essential to understand the role these may play in overcoming immunity gained by infection prior strains.

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