Cross-reactive memory T cells and herd immunity to SARS-CoV-2

Marc Lipsitch, Yonatan H. Grad, Alessandro Sette and Shane Crotty

Abstract | Immunity is a multifaceted phenomenon. For T cell-mediated memory responses to SARS-CoV-2, it is relevant to consider their impact both on COVID-19 disease severity and on viral spread in a population. Here, we reflect on the immunological and epidemiological aspects and implications of pre-existing cross-reactive immune memory to SARS-CoV-2, which largely originates from previous exposure to circulating common cold coronaviruses. We propose four immunological scenarios for the impact of cross-reactive $CD4^+$ memory T cells on COVID-19 severity and viral transmission. For each scenario, we discuss its implications for the dynamics of herd immunity and on projections of the global impact of SARS-CoV-2 on the human population, and assess its plausibility. In sum, we argue that key potential impacts of cross-reactive T cell memory are already incorporated into epidemiological models based on data of transmission dynamics, particularly with regard to their implications for herd immunity. The implications of immunological processes on other aspects of SARS-CoV-2 epidemiology are worthy of future study.

The concept of the herd immunity threshold, which refers to the fraction of the population that needs to be immune to prevent an ongoing epidemic spread of an infection, has been a major focus of research and discussion since the early days of the SARS-CoV-2 pandemic. The herd immunity threshold is reached when an infected individual infects fewer than one other person, on average. For a novel infection for which there is no pre-existing immunity, herd immunity can be generated either through infection with the pathogen or through vaccination. The effect of pre-existing cross-reactive T cell immunity on the SARS-CoV-2 herd immunity threshold has been a matter of debate[1,2], partly because of differing or unclear assumptions about the underlying biology. For SARS-CoV-2, a member of the coronavirus family that also includes the common cold coronaviruses (CCCs) HCoV-OC43, HCoV-HKU1, HCoV-229E and HCoV-NL63, the extent and nature of cross-reactivity of immune responses are variables that can influence the near and long-term trajectory of the current pandemic[3].

SARS-CoV-2 infects epithelial cells of the upper respiratory tract (URT; including the nasal passages and throat) and the lungs (bronchi and lung alveoli). These sites are involved in different aspects of SARS-CoV-2 pathology and transmission. Severe COVID-19 involves extensive lung infection, whereas SARS-CoV-2 URT infection is important for viral transmission and is associated with milder disease symptoms. Recent reports have shown that SARS-CoV-2 cross-reactive memory T cells are detectable in ~28–50% of individuals not exposed to SARS-CoV-2 (REFS[4–10]). These studies consistently found cross-reactive $CD4^+$ memory T cells in blood samples, but there was little evidence of cross-reactive $CD8^+$ memory T cells.

Memory T cells can be classified according to their anatomical location and trafficking patterns. Recirculating central memory T cells (T_{CM} cells) and effector memory T cells (T_{EM} cells) traffic through the blood and lymph nodes and are recruited to sites of infection by inflammatory signals[11]. Tissue-resident memory T cells (T_{RM} cells) permanently reside within a given non-lymphoid tissue, such as the lung or URT[12]. T_{CM}/T_{EM} cells respond more slowly to infections than T_{RM} cells and usually undergo proliferation for several days before trafficking into an infected tissue. $CD4^+$ T cells can also be divided into distinct functional subtypes. For example, T follicular helper cells (T_{FH} cells) are a specialized subtype of $CD4^+$ T cells required for B cell help and thus almost all neutralizing antibody responses[13]. T helper 1 cells (T_H1 cells) and CD4 cells with cytotoxic activity (CD4-CTL cells) are subtypes of $CD4^+$ T cells with direct antiviral activities in infected tissues. $CD4^+$ T cell-mediated memory responses to a virus may involve T_{FH} cell, T_H1 cell and/or CD4-CTL cell types.

With regard to potential cross-reactive humoral immunity, it has been found that circulating antibodies directed at the SARS-CoV-2 spike protein are uncommon in individuals not exposed to SARS-CoV-2, and, notably, cross-neutralizing antibodies appear to be very rare[14–18]. Based on animal studies to date, it appears that neutralizing antibodies are of central importance to antibody-mediated protection against SARS-CoV-2 infection. The difference between anti-spike antibody and $CD4^+$ T cell cross-reactivity is not unexpected, owing to the nature of neutralizing antibody epitopes versus peptides recognized by T cells from conserved portions of proteins. The difference in the abundance of $CD4^+$ versus $CD8^+$ cross-reactive memory T cells likely reflects the basic differences in antigen recognition between these T cell types. In a study examining T cell responses to different flavivirus species, it was found that cross-reactivity for $CD8^+$ T cells was limited to peptides carrying one or two substitutions, whereas cross-reactivity for $CD4^+$ T cells could be detected for peptides with far lower degrees of homology[19]. In sum, the cross-reactive immune memory to SARS-CoV-2 appears limited largely to one of the three major arms of adaptive immunity, the 'helper' or $CD4^+$ T cells. Critically, $CD4^+$ T cells generally do not, on their own, prevent infections. Instead, they limit disease severity, reduce the viral burden and/or limit the duration of the disease.

Although we emphasize that any functional role for cross-reactive T cell

memory in COVID-19 remains unproven[1,7], given the amount of discussion in scientific, public and political spheres, it is useful to undertake a thought experiment examining the effects on COVID-19 disease severity and herd immunity should cross-reactive memory T cells confer some form of protection against COVID-19. We propose four scenarios for the impact of cross-reactive CD4⁺ memory T cells (FIG. 1), assess their plausibility and describe how the different immunological models may impact SARS-CoV-2 transmission and herd immunity. It is possible that different scenarios could apply to different individuals. These hypothetical scenarios are discussed in order from the most subtle effects to the most substantial. The last scenario is included for completeness, although we consider it implausible.

Models of cross-reactive immunity

1. Reduction of lung burden

Cross-reactive CD4⁺ memory T cells reduce COVID-19 symptoms and lung viral load but have minimal impact on URT viral load. In this scenario, we assume that SARS-CoV-2 cross-reactive CD4⁺ memory T cells are sufficient to modulate disease severity but are not capable of eliminating the virus from the URT any faster than a primary immune response. This would be analogous to how the current acellular pertussis vaccine likely functions[20] and in line with findings from candidate SARS-CoV-2 vaccines in rhesus macaques[21,22]. This form of partial protection could be mediated by any of several mechanisms involving CD4⁺ T_{CM}/T_{EM} cells, T_{RM} cells and memory T_{FH} cells. In this scenario, we assume that the cross-reactive memory T cell population is relatively small at the time of infection, the response post infection is relatively slow and the CD4⁺ memory T cell response is unable to control the URT viral load without responses from other branches of the adaptive immune system.

Implications for individuals. Expected outcomes for individuals infected with SARS-CoV-2 who have pre-existing cross-reactive CD4⁺ memory T cells, compared with infected individuals without such memory, would include the following: (a) a reduction in the magnitude and duration of symptomatic/clinical disease; (b) no change in URT viral loads; and (c) no change in the generation of immune memory compared with people without pre-existing cross-reactive cells.

Epidemiological implications. Compared with a population including fewer individuals harbouring such memory, a population with more individuals with pre-existing cross-reactive CD4⁺ memory T cells would experience the following, all else being equal: (a) lower probabilities of hospitalizations and deaths per SARS-CoV-2 infection; and (b) no reduction, or potentially an increase, in viral spread. An increase could occur if the reduction in symptoms made infection harder to identify and trace and thus increased the frequency of undetected cases while not reducing infectiousness.

2. T_{FH} cell-accelerated antibodies

Cross-reactive memory T_{FH} cells trigger a faster and better antibody response, resulting in accelerated control of virus in the URT and lungs. In this scenario, we assume that memory T_{FH} cells facilitate a faster, better, stronger neutralizing antibody response against SARS-CoV-2 than would occur in the absence of memory T_{FH} cells. A variation of this scenario would occur if T_{CM}/T_{EM} cells, memory T_H1 cells or CD4-CTL cells were the functionally important CD4⁺ memory T cell compartment. After activation and proliferation of these T cells over a period of days, control of the SARS-CoV-2 virus in the lung and URT would follow. Data consistent with both of these scenarios have been observed for influenza[23–25].

Implications for individuals. Expected outcomes for individuals infected with SARS-CoV-2 who have pre-existing cross-reactive CD4⁺ memory T cells, compared with infected individuals without such memory, would include the following:

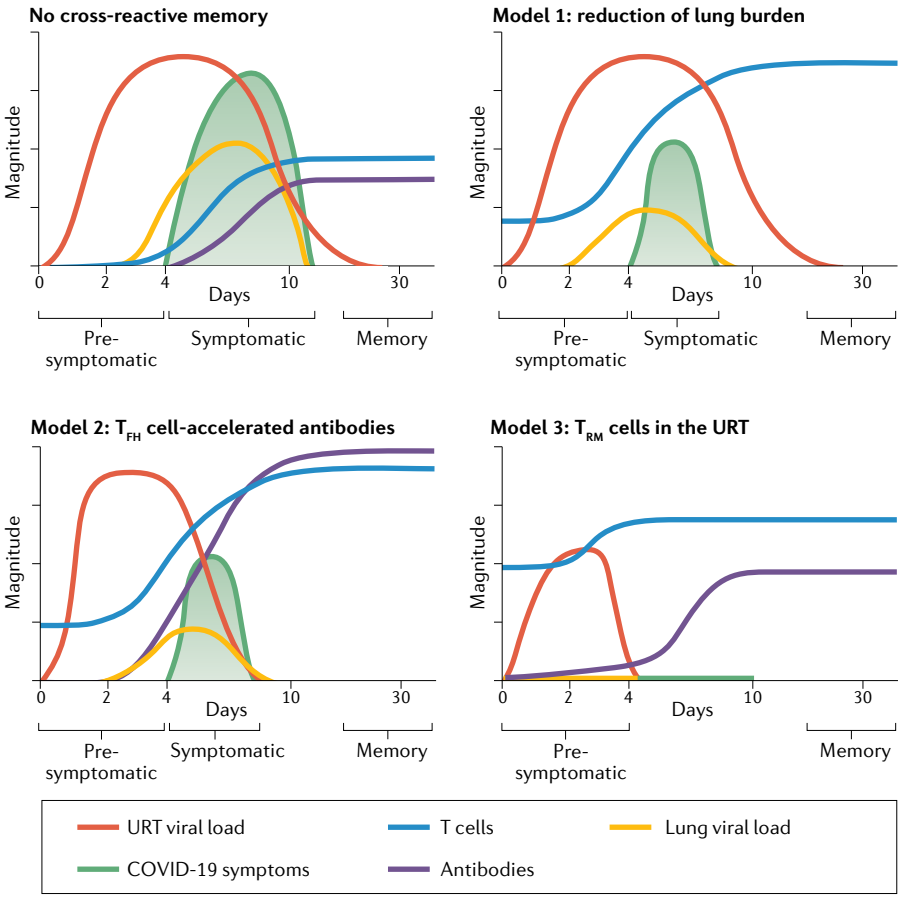

Fig. 1 | **Schematic models of the three major scenarios wherein cross-reactive CD4⁺ memory T cells have a positive impact on control of SARS-CoV-2 replication in an individual and reduce COVID-19 disease severity.** Timelines of viral burden in the lungs and upper respiratory tract (URT) and of immune responses, which differ according to the magnitude and type of pre-existing cross-reactive CD4⁺ T cell memory. Model 1 makes no specific prediction about antibody response kinetics or magnitude, because it could be mediated by different types of immune response with equivalent disease outcomes (see main text). Under scenario 4, there would be no infection in individuals with cross-reactive immunity (scenario therefore not shown). Each of these models is currently hypothetical for SARS-CoV-2. T_{FH} cell, T follicular helper cell; T_{RM}, tissue-resident memory cell.

(a) a reduction in the magnitude and duration of symptomatic disease, all else being equal (for example, an individual of a given age and co-morbidities, exposed to a given viral inoculum, would tend to have lower severity — as measured by, for example, risk of hospitalization, ICU or death — with such T cell memory than without); (b) SARS-CoV-2 viral loads in the URT would not be affected during the pre-symptomatic phase, but would be somewhat reduced thereafter, because of the intermediate kinetics of the immune response; and (c) robust immune memory would likely be generated.

Epidemiological implications. Compared with a population including fewer individuals harbouring such memory, a population with more individuals with pre-existing cross-reactive $CD4^+$ memory T cells would experience the following, all else being equal: (a) fewer hospitalizations and deaths; (b) a modest to moderate reduction in viral spread, as the pre-symptomatic period plays a substantial role in spread[26] — the reduction in URT viral load under this scenario would mean a modest to moderate reduction in spread in a population in which cross-reactive T cell memory was relatively common; and (c) greater heterogeneity (assuming a minority have such cross-reactive memory) in infectiousness, as variability between those with and without memory would enhance overall variability. Heterogeneity in infectiousness, all else being equal, increases the chance that a virus introduced into a population will fail to spark a large epidemic (although this can be overcome by multiple introductions)[27,28].

3. T_{RM} cells in the URT

Cross-reactive $CD4^+$ T_{RM} cells at the site of infection enable rapid control of virus in the URT and lungs. This scenario would occur via $CD4^+$ T_{RM} cells in the URT at the site of infection. These $CD4^+$ memory T cells would restrict viral replication in the URT in the days after infection and possibly also restrict viral replication through the rapid activation of the innate immune system. In the case of SARS-CoV, the causative agent of severe acute respiratory syndrome, an intranasal vaccine formulated to induce $CD4^+$ T cell responses elicited airway $CD4^+$ T_{RM} cells that provided substantial protective immunity in mice, but the protection was against fatality and did not prevent early SARS-CoV viral replication[29]. The $CD4^+$ T_{RM} cells controlled virus replication over a period of ~5 days.

Implications for individuals. Expected outcomes for individuals infected with SARS-CoV-2 who have pre-existing cross-reactive $CD4^+$ memory T cells, compared with infected individuals without such memory, would include the following: (a) a short, asymptomatic infection; (b) low SARS-CoV-2 viral loads, with a rapid decline to undetectable levels within days; and (c), possibly, reduced generation of new memory to SARS-CoV-2, owing to the limited antigen load.

Epidemiological implications. Compared with a population including fewer individuals harbouring such memory, a population with more individuals with pre-existing cross-reactive $CD4^+$ memory T cells would experience the following, all else being equal: (a) fewer hospitalizations and deaths, owing to modified symptoms; (b), potentially, a considerably lower degree of spread owing to lower viral loads and shorter duration of shedding, which both presumably contribute to a lower basic reproduction number (R_0)[26,30]; and (c), even more than in scenario 2, enhanced heterogeneity in infectiousness.

4. Transient infection

T_{RM} cell immunity 'blitzes' viral replication in the URT. This scenario is an unlikely, extreme variation of scenario 3. Immunologically, this outcome would be unprecedented. 'Sterilizing immunity' refers to antibodies preventing any cells from being infected. Given that T cells can only respond after cells are infected, the closest T cells could come to sterilizing immunity would be a massive T_{RM} cell 'blitz' in the tissue, leading to the elimination of all infected cells within a day of the initial infection, at the portal of entry. Such T cell events have only been reported in the presence of large numbers of $CD8^+$ T_{RM} cells in certain animal models[12]. There is no example where this has been observed for $CD4^+$ T cells, and the available data indicate that $CD4^+$ T_{RM} cells can only blunt infection over a period of several days[31,32]. This is also consistent with the fact that $CD8^+$ T cells recognize antigens presented on essentially any infected cell (MHC class I presentation), whereas $CD4^+$ T cells recognize antigens presented by only a subset of cells (MHC class II presentation). As noted above, in the case of SARS-CoV, a $CD4^+$ T cell intranasal vaccine elicited airway $CD4^+$ T_{RM} cells that provided substantial protection from the disease in mice, but only eliminated virus replication after ~5 days[29], not supporting scenario 4.

As a thought experiment, if the pre-existing $CD4^+$ T_{RM} cell immunity was so extreme as to preclude significant viral replication, seroconversion (that is, a de novo antibody response to SARS-CoV-2) would not occur. Such individuals would not be detectable by virological or serological diagnostic tests and would not shed virus; effectively, these individuals would be immune to infection and not reported as cases. This appears inconsistent with human coronavirus challenge studies. In human CCC challenge–rechallenge experiments, even with the same or closely related CCC strains and the benefit of antibody-mediated immunity[33,34], reinfection was frequently observed (although not necessarily symptomatic disease), making it implausible that cross-reactive CCC T cell memory alone would routinely abort SARS-CoV-2 infection.

Epidemiological observations are also inconsistent with widespread immunity to infection as proposed by this scenario. Two ship-based outbreaks reporting cumulative attack rates of 67.9% and 85.2% are inconsistent with high levels of pre-existing immunity to infection in the on-board populations[35,36]. Considering this epidemiological evidence alongside immunological precedent, scenario 4 is highly unlikely for SARS-CoV-2, particularly given the relatively low levels of cross-reactive $CD4^+$ memory T cells observed in blood samples so far. A recent COVID-19 study observed approximately 3 SARS-CoV-2-exposed (not PCR-confirmed) potentially asymptomatic cases with T cell responses in the absence of seroconversion[10]. Although there has been extensive discussion in the public arena, and in public health circles, of whether a large population of seronegative previously SARS-CoV-2-infected people exists, if one excludes the issue of poor-quality serological kits, the preponderance of data supports the conclusion that the vast majority of SARS-CoV-2-infected individuals do seroconvert, at least for a duration of months[4,14,37–41]. Quantitatively, these estimates range from 99% in a New York City study of 624 PCR-confirmed cases to 91.1% in an Icelandic study of 1,797 patients[37,40]. Thus, the frequency of SARS-CoV-2 infections resulting in a T cell response alone appears to have a ceiling of 1–9% of total SARS-CoV-2 infections, and it is likely that those outcomes reflect biology other than scenario 4 (for example, a very low viral inoculum).

Epidemiological implications. Under this scenario, compared with a population including fewer individuals harbouring pre-existing cross-reactive $CD4^+$ memory T cells, all else being equal, the following would occur: (a) the maximum proportion who could become infected would be lower; and (b) the herd immunity threshold would be lower. These implications differ significantly from scenarios 1–3.

Existing epidemiological knowledge

How does the recent discovery of cross-reactive T cells against SARS-CoV-2 in some individuals change our understanding of the pandemic? To find an answer to this question, several considerations are crucial. First, whereas scenario 1 suggests that T cell cross-immunity might increase viral spread, and scenarios 2, 3 and 4 suggest that T cell cross-immunity would reduce viral spread, the empirical data obtained in the early days of the pandemic (and since then) incorporate these aspects of virus–host interaction. It is 'baked in' to the data: the estimates of contagiousness (R_0), the time course of infection and the range of severity parameters all incorporate the existence of whatever cross-immunity was present[3].

Second, under scenarios 1–3 as described above, T cell immunity does not prevent infection but, rather, can modulate the time course of disease and infectiousness. Therefore, cross-immunity of this sort is not immunity to infection and is not expected to 'supplement' herd immunity to SARS-CoV-2 infection. Similarly, it has been noted that heterogeneity in susceptibility to becoming infected can lower the herd immunity threshold, for a given basic reproductive number[42,43]. Again, under scenarios 1–3, T cells are likely to augment the heterogeneity in infectiousness of those who do get infected, but, unlike heterogeneity in susceptibility, heterogeneity in infectiousness does not change the final size of epidemics and, by analogy, does not change the herd immunity threshold[44]. In sum, under scenarios 1–3, the discovery of cross-reactive T cells should not substantially change projections of disease dynamics in populations or, specifically, of the proportion of the population who will become infected before transmission wanes. By contrast, under scenario 4, the herd immunity threshold would be lower than in current predictions, which are based on estimates of R_0 and the assumption that all individuals are at equal risk of infection. Immunological knowledge and epidemiological data make scenario 4 very unlikely. In summary, the discovery of cross-reactive T cell immunity should not change our estimates of R_0 or the herd immunity threshold in any given population, although differences in the prevalence of cross-reactive immunity between populations could cause a variation in R_0 and the herd immunity threshold between such populations.

Having cleared up these misapprehensions, there are numerous fascinating open questions for future research on both the individual level and the epidemiological effects of cross-reactive T cells. At the individual level, distinguishing among scenarios 1–3 discussed above is particularly important, so that we can understand what role, if any, these memory T cells play in modulating the time course of disease and viral shedding. Cross-reactive T cell memory may help to explain the great variation in COVID-19 symptomatic/asymptomatic disease outcomes observed in SARS-CoV-2-infected individuals. Epidemiological studies will likely play a role in this effort[35], in this case supplementing studies of clinical outcome with detailed studies of (ideally, pre-exposure) T cell specificities. Vaccine trials, which already gather blood samples from many participants, may be ideal settings in which to nest such studies, whereby after completion of the study those in the control arm who did become infected and had varying levels of infection severity can be compared. For example, it could be determined whether, after adjusting for age and co-morbidities, the severity of COVID-19 symptoms or viral shedding was different in those with and without cross-reactive T cells. Lastly, it remains an open possibility that cross-reactive memory T cells may instead exacerbate COVID-19 disease, owing to low T cell receptor avidities or aberrant T cell polarization, which is a serious concern. Findings on each of these topics above would expand our scientific knowledge and potentially improve prognostic and risk-stratification accuracy for patients with COVID-19.

If, indeed, cross-reactive T cells do reduce COVID-19 disease severity and/or SARS-CoV-2 shedding, it is possible that different populations (geographical or demographic) may differ with regard to disease severity or contagiousness because they have different degrees of prior exposure to coronaviruses[6] and thus different degrees of T cell-mediated cross-reactive immunity. This would mean that R_0 was lower in populations with more cross-reactive immunity, adding one further reason why R_0 is not a 'constant of nature' but a function of both the virus and the host population and needs to be assessed locally to make reliable local predictions. Although it would be challenging to assess these effects at a whole-population level, and many confounding factors might exist, it would be informative to understand whether the extent of cross-reactive memory T cells varies dramatically by geography or by factors such as age. If so, it would then be important to understand whether this variation correlates with the differences that have been observed for COVID-19 severity or SARS-CoV-2 spread.

It is also important to point out that the potential influence of $CD4^+$ T cell memory does not explain all differences observed for COVID-19 disease severity, under any model. Other factors such as co-morbidities, advanced age, sex or the size of the naive T cell repertoire play important roles in modulating COVID-19 disease severity[41,45,46].

Lastly, these proposed models are also relevant to consider for other viral infections and situations. For example, for vaccine-induced immunity to SARS-CoV-2, in the absence of sterilizing immunity, several of the proposed models of how cross-reactive T cell memory could provide partial protective immunity may exist in parallel with the immunity induced by a vaccine.

Conclusion

Cross-reactive T cell memory may or may not affect COVID-19 disease severity in individuals. However, given the implications of the possibility, it is worth considering specific immunological and epidemiological scenarios. Four distinct immunological scenarios were considered herein. In each of the three scenarios that we consider plausible, the reduction in viral spread potentially afforded by pre-existing immunity is already accounted for by the empirical observational data available and factored into epidemiological models of spread and herd immunity — with the key caveat that if T cell immunity varies geographically and affects transmission, the extrapolation of epidemiological parameters across populations may not be fully valid. However, in any scenario wherein cross-reactive T cell memory affects SARS-CoV-2, there would still be substantial implications for understanding disease severity and risk stratification, and, looking forwards, there are numerous immunological and epidemiological relationships that should be explored for their implications for the COVID-19 pandemic as well as for the post-pandemic era.

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Author contributions
The authors contributed equally to all aspects of the article.

Competing interests
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