Title

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Journal

The Journal of Immunology, 205(9)

ISSN

0022-1767

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Publication Date

2020-11-01

DOI

10.4049/jimmunol.2000839

Peer reviewed

HHS Public Access

Author manuscript

J Immunol. Author manuscript; available in PMC 2021 November 01.

Published in final edited form as:

J Immunol. 2020 November 01; 205(9): 2342–2350. doi:10.4049/jimmunol.2000839.

Antibody Responses to SARS-CoV-2: Let's stick to known knowns

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Abstract

The scale of the SARS-CoV-2 pandemic has thrust immunology into the public spotlight in unprecedented ways. In this article, which is part opinion piece and part review, we argue that the normal cadence by which we discuss science with our colleagues failed to properly convey likelihoods of the immune response to SARS-CoV-2 to the public and the media. As a result, biologically implausible outcomes were given equal weight as the principles set by decades of viral immunology. Unsurprisingly, questionable results and alarmist news media articles have filled the void. We suggest an emphasis on setting expectations based on prior findings, while avoiding the overused approach of assuming nothing. After reviewing antibody-mediated immunity after coronavirus and other acute viral infections, we posit that, with few exceptions, the development of protective humoral immunity of more than a year is the norm. Immunity to SARS-CoV-2 is likely to follow the same pattern.

Introduction

The SARS-CoV-2 pandemic has thrust immunology into the public spotlight in unprecedented ways and discussions of antibody testing have become commonplace in the public press, prompting us to write this brief review to put our understanding of humoral immunity to infections in general into the context of infection with this newly emerged virus. As of the writing of this article, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected close to 18 million people and killed over 675,000. The magnitude of this global pandemic is unprecedented in our lifetime. As a result, this virus

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has received unprecedented attention from scientists and the public. As of this writing, nearly 30,000 Pubmed-indexed articles have already been published about SARS-CoV-2 and COVID-19, the disease it causes. Given that the virus was first reported in December 2019 (1, 2), the pace of investigation and publications makes SARS-CoV-2 the most-studied virus in history. Navigating, filtering, and communicating this enormous amount of information to the public and media has fallen to journal editors and scientists from a variety of diverse disciplines. These are tasks for which few of us were prepared. The implications of what is said and how it is interpreted and publicly scrutinized are greater than anything we have faced to date, and with good fortune, will ever face again.

Communicating with the public, decision-makers, and media

A common refrain in publications, grant applications and interviews is, “Process X is poorly understood.” Science is ultimately a process of reducing uncertainty. Absolute certainty is rarely possible, so expressions of a nuanced approach to addressing a particular question, and revealing a lack of detailed knowledge, are perceived by other scientists as markers of mature, high-integrity work and as providing a sound rationale for studying the details of a problem in depth. Yet, in the context of the COVID-19 pandemic, such statements are often misleading and can be outright harmful. In science, prior knowledge usually sets a range of expectations around which uncertainty is narrowly centered. As scientists, we implicitly understand the nuance and meaning of such statements. Yet at the beginning of the crisis when many, including some of the authors of this perspective and review, were called into interviews with the media, the unintended effects of our standard ways of communicating with other scientists became clear.

It is true that the kinetics of the immune response to SARS-CoV-2, the immunophenotypes of protective innate and adaptive cells, and other key details are poorly understood. Yet, few immunologists would consider it likely that infected subjects would develop no immunity after viral clearance. It is also true that the precise duration of immunity after infection is unknown, but it is unlikely that it lasts only for a few weeks. As we expressed uncertainty, per our normal convention, highly unlikely outcomes were often portrayed by the media as equally likely to those we expected, based on the experience we gained from other viral infections. Public health organizations including the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) have made similar problematic ‘absence of evidence’ statements regarding facemasks, immunity after infection, and the efficacy of testing asymptomatic individuals on college campuses (3–5). These announcements have had, and still have real-world detrimental consequences on efforts to contain community transmission. They may also engender unwarranted skepticism and hesitancy regarding vaccines and therapeutics, once such options emerge.

Having learned from some of our own misadventures in clearly communicating our thinking, we suggest subtle but meaningful adjustments. Consider the statement, “We don’t know how long immunity will last.” As a comparison, consider the alternative statement, “We don’t know for sure how long immunity will last, but if it is anything like the first SARS coronavirus, it will last for at least several years.” Both statements are factually correct, but the impact on the public is markedly different. We have taken to favor the latter approach.

However, to successfully employ this strategy, a critical assessment of the primary data and antecedent literature is essential to form the basis of our answers. What is the evidence that immunity and resistance to subsequent infection are elicited by SARS-CoV-2 infections, and how long is immunity likely to last? How can we apply what we have learned about antibody responses to the interpretation of diagnostic and serological tests? How likely is it that vaccines can protect the general public, as well as vulnerable populations? These questions arise often in daily discourse in contexts we will discuss below. We identify relevant examples in the literature that can provide the basis for setting expectations and answering these questions.

Defining ‘immunity’

To begin, a consistent definition of ‘immunity’ is needed. For the purposes of this article, the operational and objective definition of immunity is a state that increases the inoculum required to cause infection, disease, and transmission. Thus, a loss of immunity implies equal susceptibility to acute viral infections as if one were immunologically naïve. Though in this review we focus on humoral immunity with an emphasis on long-lived plasma cell-derived serum antibodies, many cell types contribute to resistance and immunological memory. Subsets of both memory B and T cells establish local residence at the sites of infection, while others circulate to patrol for distal exposures (6, 7). Natural killer cells form a version of cytokine-competent memory cells (8, 9), and myeloid lineages can maintain an epigenetically primed state for long periods of time (10). The collective sum of these and other components is thus what comprises immunity.

Initial confusion about immunity and re-infection by SARS-CoV-2

During the early stages of the pandemic, reports began to surface of patients testing positive for viral RNA, then negative, and then positive again in relatively short succession (11). The largest number of such subjects exhibiting such a pattern was reported by the South Korean Centers for Disease Control and Prevention (KCDC). A subset of such patients anecdotally reported either continued or new symptoms at the time of the last PCR positive result. Though neither the KCDC, nor many scientists interviewed, considered it likely that these patients had been re-infected in such a short period, this nuance was lost in the news media. Then the WHO issued the following announcement: “there is currently no evidence that people who have recovered from COVID-19 and have antibodies are protected from a second infection.” Unfortunately, these agnotological statements can provide fuel for vaccine skeptics.

Meanwhile, scientists at the KCDC and around the world accumulated evidence that re-infection did not explain these observations, and immunity was almost certain to ensue clearance of the primary infection. Extensive studies by the KCDC demonstrated that infectious virus was undetectable in patients who had tested PCR positive after a negative result (11). Contact tracing of relatives following the return of the patients to their homes revealed not a single instance of transmission (11). These data suggest a few possible explanations for the unusual PCR patterns. First, the second PCR result represents a false negative. Indeed, false negative results can approach 30% of such tests, so mathematically it

would be expected that these types of patterns would emerge with some frequency (12). In this case, the patient presumably had not yet cleared the infection in the first place, explaining a subsequent positive result. A corollary to this interpretation is that viral replication may still have been ongoing, but the presence of neutralizing antibodies prevented subsequent culture and community transmission. Second, the last PCR assay might have simply detected viral genomic remnants or non-infectious particles released from dying cells rather than bona fide infectious virus. Consistent with this interpretation, a similar recent study demonstrated that RNA fragments, rather than intact viral genomes were recovered through sequencing in such patients, while culturable virus was not retreivable, nor could virus transmission be detected (13).

Immunity and resistance to re-infection

Concomitantly, several groups reported clear evidence of immunity after SARS-CoV-2 infection and clearance. Seroconversion and neutralizing antibody production, which is the best correlate of protection for many infections and almost all vaccines (14), were observed in nearly all convalescent patients with confirmed COVID-19 (15). For most acute viral infections and following vaccination, the presence of neutralizing antibodies (nAb) is a clear functional correlate of immunity (14), and almost certainly provides at least partial resistance to subsequent infections. Indeed, the first convalescent plasma passive transfer studies in hospitalized patients were also reported around this time (16, 17). Though these studies were small and did not have placebo groups, viral loads were sharply reduced and patient outcomes improved shortly after the plasma transfers. Subsequent convalescent plasma studies in other institutions have continued to suggest a benefit, especially if administered early (18, 19). Another piece of evidence came from experimental infection of macaques. Two weeks after clearance of the first infection, these macaques became fully resistant to high-dose re-challenge with SARS-CoV-2 (20, 21). Collectively, these studies demonstrated what one would have expected, namely that clearance of an acute viral infection leaves one immune.

It is entirely possible that some individuals do not seroconvert after infection, at least to certain viral antigens, particularly if they rapidly cleared a localized upper respiratory tract infection. Perhaps in these cases, the durability of immunity is brief and susceptibility to reinfection is possible. However, the percentages of individuals not seroconverting, claimed by some studies, seem unlikely, ranging from 10–80% (22–24), often relying on assays with unclear sensitivities and/or indirect estimates by including individuals who did not have PCR-confirmed infections. Other rigorous studies have shown that seroconversion is almost universal after confirmed infections, even when the disease is mild (15, 25–28). Given the evidence, a statement of, “there is no data that COVID-19 recovered patients who develop antibodies can be re-infected” would have conveyed a message of assurance rather than hysteria, and would be entirely consistent with the accumulated evidence.

Challenges with antibody testing and data interpretation for SARS-CoV2

Although the original WHO statement on antibodies and reinfection was off-target in our opinion, a legitimate concern is the degree to which a positive antibody test indicates that one is immune. Beginning in March of 2020, the market became flooded with point-of-care

serological tests to define prior SARS-CoV-2 exposure and, presumably, immunity. These products were allowed to be sold under emergency use authorizations by the Food and Drug Administration (FDA), a mechanism employed in response to the initial shortage of RT-PCR tests for viral RNA. Yet, many of these tests performed poorly, reaching false positive rates that approached the true seroprevalence of the target population. Independent validation at the University of California, San Francisco, revealed that the majority of these assays were unreliable, with poor specificity and sensitivity compared to conventional ELISAs (29). The FDA has subsequently removed many of these products in the U.S. Unfortunately, the distinction has been lost between these faulty point-of-care lateral flow assays and reliable standard serological ELISAs, some of which perform exceptionally well and correlate uniformly with virus neutralization titers (26, 27, 30). Such doubt has been amplified in the news media and risks depriving infectious disease epidemiologists of a valuable tool in monitoring community transmission, and also physicians treating COVID-19 subjects of convalescent plasma, proven to contain protective anti-SARS-CoV-2 antibodies.

One of the intended uses of many of the point-of-care tests was to distinguish the timing of infection based on antibody isotype. As primary B cell responses often begin with secretion of IgM, it was assumed that production of this antibody isotype would demonstrate recent, and potentially ongoing infection and virus shedding. Conversely, IgG would represent later phases of infection and convalescence. This interpretation has practical consequences, as some employers, including the Banner-University of Arizona Medical Center-Tucson, require quarantine of employees who test positive for IgM, but dispense with this requirement if SARS-CoV-2-specific IgG is detected.

Fundamentals of B cell responses to acute viral infections

Extrafollicular and germinal center-derived antibody responses to infections shape the serum antibody titers

Despite the broad use of IgM/IgG ratios in the clinics as a sign that an infection is recent (IgM only), ongoing acute (IgM and IgG) or occurred some time ago (IgG only), such interpretation of the serological data is an oversimplification of humoral immunity to infections, as opposed to model antigens. B cell plasmablasts develop rapidly following an acute infection and these responses provide much of the earliest measurable wave of serum antibodies. In contrast to the later-developing plasma cells developing from germinal center responses, which are mostly Ig-class-switched, these “extrafollicular” B cell responses produce IgM as well as class-switched IgG and IgA, depending on the involved lymph tissue and the cytokine milieu induced by the infection (Figure 1). Respiratory tract infections induce IgM, IgG and IgA, as indeed found for patients infected with SARS-CoV-2 (15, 31, 32). Based on current understanding of these mostly T-dependent responses, there is no expectation that IgM responses necessarily precedes class-switched responses, as class-switching is rapidly induced during the process of B cell activation and clonal expansion (33–35), and thus prior to their differentiation to IgM or IgG-secreting cells. Given that extrafollicular B cell responses do not seem to require continued “T cell help” (36), production of IgM might be favored, as induction of AID, the enzyme facilitating class-switch recombination, is strongly induced via interaction through CD40-CD40L. What has

been appreciated more recently is that B cell activation in the extrafollicular compartments of secondary lymph tissue can lead to the development of non-switched IgM memory B cells (37) and may even lead to long-lived IgM responses by plasma cells secreting IgM for extended periods of time (38, 39), again making a distinction between acute and later-stages of infection based on IgM/IgG ratios impossible.

In acute infections, such as a respiratory tract infections with influenza virus, IgM responses are induced and then rapidly lost, because IgM secreting LLPC are not induced. As the acute extrafollicular response resolves and the short-lived IgM and IgG or IgA-secreting plasmablasts die, germinal center-derived plasma cells replace these early-secreting cells, most if not all secreting class-switched antibodies, such as IgG and IgA. Since the half-life of IgM is only in the order of a few days (40), in contrast to that of IgG, which is in the order of 3–4 weeks depending on the isotypes or subclasses, serum IgM levels rapidly disappear. Thus, it is not surprising to see that IgM and IgG titers have been shown to rise together, or in some cases the IgG or IgA responses may even precede that of IgM in patients infected with SARS-COV-2 (15, 31, 32). The results suggest that, as expected, SARS-CoV-2 induces robust extrafollicular responses in the respiratory tract draining lymph tissue, driven in part by the local elaboration of inflammatory cytokines. Consistent with these conclusions, a recent study provides support for strong extrafollicular responses to SARS-CoV-2 (31). Their increased and possibly continued presence in severely ill patients underscores the nature of this humoral response as an “emergency supply system”, ensuring the rapid production of protective antibodies, both switched and non-switched. Asymptomatic patients and those with mild disease exhibit lower overall antibody responses, but do also possess neutralizing titers (41–43). As convalescence begins, B cell responses shift from “emergency supply” to the development of long-lived responses in germinal center responses, which are geared towards developing protection from future re-encounters. We do not currently understand what drives the shift from the extrafollicular to the germinal center response, but based on preliminary data inflammatory signals are critical for the development of the EF response (Lam, J.H. & Baumgarth, N., in preparation).

Within the germinal center reaction, B cells undergo somatic hypermutation of their immunoglobulin genes and selection for those variants with higher affinity for antigen. High affinity variants are then fated for either memory B or plasma cell differentiation. Generally, as antibody affinity increases over time, so too does the lifespan and secretory capacity of plasma cells (44–46). Consequently, relatively few plasma cells are required to confer protection against subsequent infections, provided antibodies are made against the key viral epitopes. As an example, passive transfer of a single microliter of West Nile virus immune serum, corresponding to just 3 antigen-specific long-lived plasma cells, is enough to protect a naïve mouse from an otherwise lethal inoculum (47). Plasma cell lifespan is variable based on the specific vaccine or infection, but as a general rule, the duration of antibody production is very long after natural exposures, as seen in responses to acute viruses such as mumps and measles (48). Long-lived plasma cells (LLPCs) are the sources of this durable antibody production (49–54). Humoral immunity to chronic infections such as those caused by HIV and HPV, where viral antigens can persist in the host, are more complex (55). Given the acute nature of SARS-CoV-2 infections, chronic infections will not be discussed further here.

Humoral immunity in respiratory tract

Based on existing data on other acute respiratory tract infections, one would thus expect reductions or even disappearance of serum IgM and IgA responses to SARS-CoV-2 over time, while IgG titers should wane slower and remain elevated for extended periods of time (56). Unlike IgA, which is the dominant isotype in the upper respiratory tract, IgG is often considered to have minimal access to mucosal sites, yet this is not entirely accurate. First, although IgG cannot bind to the poly-Ig-receptor, which transcytoses dimeric IgA, FcRn can serve this function and promote IgG transport into lumenal secretions (57). As demonstrated by the highly successful intramuscular human papillomavirus vaccine, IgG can protect against mucosal infections through a combination of transcytosis and transudation (58). Second, serum IgA is usually monomeric rather than dimeric (59), and thus is unlikely to support lumenal defenses. Third, only the upper respiratory tract and large bronchi contain mucosa. The parenchyma of the lower respiratory tract lacks a mucosa, its barrier inhibiting oxygen exchange, and correspondingly, antiviral humoral responses in the lung are dominated by IgG rather than IgA (60). Thus, the rapid waning of IgA responses observed in COVID-19 patients (31, 61, 62), is not a priori a cause for concern in the background of stable neutralizing IgG titers. This IgG produced by LLPCs also have undergone extensive somatic hypermutation and affinity maturation, and can therefore provide strong protection against homologous virus challenges. The successful use of convalescent plasma from previous COVID-19 patients for the treatment of severely ill patients supports the conclusions that when patients have had robust infections with SARS-CoV-2, they will develop germinal center responses, and thus protective humoral immunity that can be expected to last for extended periods of time. Patients with only mild and localized infection in the upper respiratory tract may develop local tissue-resident antibody and/or cell-mediated immunity (7, 63), which would not be captured by serological testing. Critically ill individuals with ongoing dysregulated inflammatory responses may not shift from extrafollicular to germinal center responses and maybe unable to support germinal center responses.

Role of memory B cells in viral infections

Memory B cells tend to emerge earlier in the germinal center response, encode lower affinity antibodies than their long-lived plasma cell counterparts, and encompass a number of functionally distinct subsets (37, 64–70). Immunoglobulin class-switched memory B cells are thought of as the first responders when pathogens evade pre-existing serum antibodies (37). This is likely because these cells can bypass the requirement for T cell help in response to viral infections (71). In mice, these memory B cells can be further distinguished by expression of the markers CD80 and PD-L2 (37, 64, 66, 67). Importantly, similar to responses seen during a primary infection, these memory B cells generate the transiently-induced extrafollicular “emergency” antibody responses, likely driven by the same inflammatory signals that initiated this responses during a primary infection, but now derived from a previously selected and clonally-expanded population of B cells. Recall responses may also be driven in part by transcriptional programs that bias towards transience more so than primary responses (72–74). The distinction between primary and memory B cell responses becomes particularly important in the context of prior coronavirus studies.

Duration of humoral immunity after coronavirus and other acute viral infections

Duration of immunity to common coronaviruses

Infectious coronaviruses with human tropism can be stratified into alpha and beta lineages. Whereas the most pathogenic coronaviruses, including MERS, SARS-CoV-1, and SARS-CoV-2 fall within the latter, so too do less dangerous and more common strains, including OC43 and HKU1 (75). The most common alpha coronaviruses include 229E and NL63, both of which cause a relatively mild “cold”. Because of the mildness of symptoms caused by the common human coronaviruses, much of our information has come from early challenge studies of human volunteers using live virus, dating back to the 1960s and before modern tools to distinguish genotypes were available (76).

The seroprevalence for the common human coronaviruses is well over 90% (77). Thus, it is not feasible to identify immunologically naïve adults for challenge studies. Adding further complications, there is substantial serological cross-reactivity across different coronaviruses within and even across alpha and beta lineages (78). Thus, challenge studies in these settings almost certainly measure memory rather than primary responses, without a means to determine whether the challenges are homologous or heterologous. In early studies, challenge of volunteers with the 229E coronavirus strain led to complete resistance to re-infection and shedding by the same virus for at least one year (79). Of note, despite substantial serological cross-reactivity, this same level of resistance was not observed when subjects were re-challenged with heterologous alpha coronaviruses with similarity to 229E (79). These data emphasize the important distinction between viral serotypes and genotypes. Durable immunity to homologous strains is almost certain; immunity to heterologous strains is less certain.

A widely cited study followed these early experiments in which antibody titers were followed after experimental challenge of human volunteers, demonstrating that antibody production returns to near pre-challenge levels after only 1 year (80). This observation has widely been interpreted as evidence that immunity to coronaviruses is intrinsically transient. Yet, this interpretation should be tempered for several reasons. First, upon a second challenge one year after the first, none of the subjects developed symptomatic disease and viral shedding was transient and minimal. Second, the pre-existing baseline titers against 229E were high for all experimental groups prior to the challenge. In the productively infected subjects, antibody kinetics rose and fell quickly before returning to slightly above this baseline, consistent with the expectation of memory B cell responses. Importantly, the group of subjects that could not be productively infected maintained very high antibody titers that did not change before or after attempted infection, suggesting very durable protective humoral immunity. Finally, as with all challenge experiments, the experimental inoculum was likely higher than that which occurs in natural exposures. Together, these findings imply that immunity to homologous common coronaviruses lasts for longer than the single year that is often stated in review articles and in the media.

Why, then, do we keep getting infected with common coronaviruses so often (81, 82)? The answer may lie in the underappreciated genetic diversity of coronavirus strains (83–85). The mutation rate for both SARS-CoV2 and common coronaviruses is relatively low (for NL63, the estimated substitution rate is 3×10^{-4} per site per year in the Spike protein), but some of the common coronaviruses have been circulating amongst the human population for an estimated 1000 years (83, 86). Given the near universal seroprevalence for common coronaviruses, presumably there exists intense selective pressure to evade these defenses. Indeed, early studies suggested that coronaviruses of the same serogroup may be able to escape heterologous immunity (79). The extent to which prior coronavirus infections impact heterologous immunity to SARS-CoV-2 remains under investigation (22, 25, 87).

Duration of immunity to SARS-CoV-1 and SARS-CoV-2

Intentional challenge studies are of course not ethical for deadly strains such as MERS and SARS-CoV-1. Thus, surrogates must be relied upon to estimate the duration of immunity. Studies on SARS-CoV-1 demonstrated that virus-specific IgG antibody titers peaked at month 4 and their geometric mean reciprocal titers declined 7-fold and 10-fold at months 24 and 36, respectively (88). Based on these data, it was concluded that antibody production lasts for only 1–3 years after clearance of infection. These estimates, however, are problematic when extrapolated from the early phases of the response when many short-lived plasma cells are dying, which as discussed provide the early wave of antibodies. For most acute challenges, a relatively stable nadir is eventually achieved of antibodies continuously produced by long-lived plasma cells (49). Thus, the decay of antibody production during the course of a response is not linear because it is contributed by distinct plasma cell subsets (both short-lived and long-lived), and the duration of immunity can therefore only be calculated over longer periods of time (Figure 1). Indeed, recent studies reported that SARS-CoV-1-neutralizing antibodies could still be detected 12–17 years after the infection was resolved (89, 90). Interestingly, antibody titers were low as measured by standard ELISAs, demonstrating that very small quantities of high-affinity antibodies can prevent infection, at least *in vitro*. Because SARS-CoV-1 infected relatively few people and no longer circulates, there is no way to epidemiologically determine if people resist re-infection so long into convalescence.

The SARS-CoV-2 pandemic began only a few months ago. Thus, by definition, humoral responses in those infected are still in the early phases. Several SARS-CoV-2 studies have suggested rapid waning of immunity and antibody responses against the nucleocapsid protein, especially in those who recovered from mildly symptomatic disease (41, 91). For the same reasons as discussed above for SARS-CoV-1, such conclusions are premature in our view. All antibody responses, even exceptionally durable ones such as against measles, show an initial decline not inconsistent with what has been observed for SARS-CoV-2 thus far (48). Moreover, neutralizing antibodies to SARS-CoV-2, which presumably bind the spike protein, remained very high in the same study (41). The discrepancy might reflect differences in either assay sensitivity or antibody responses to nucleocapsid vs. spike protein. Based on the fundamental principles of B cell response regulation that we outlined above, we consider it very unlikely that immunity to SARS-CoV-2 would be lost already. At present, serum antibody titers are clearly important, but a comprehensive assessment of

protective SARS-CoV-2 immunity will be more informative. It is likely to include both humoral and cellular measurements that will include mucosal and serum antibodies as well as cellular measures that include circulating and tissue resident memory T and B cells.

Durability of antibody responses to other acute respiratory viruses

Aside from coronaviruses, a wealth of knowledge has also been gained for other acute respiratory infections. Respiratory syncytial virus (RSV) is often cited as an example of a natural infection conferring only short-term immunity. Yet, a review of the literature suggests more complexity than is appreciated. After infection, neutralizing antibodies do indeed decline initially (92), as is seen in all humoral responses irrespective of the ultimate duration of immunity (48). Yet when followed over the course of several years, protection against subsequent infection is the norm and later timepoints suggest a relatively stable nadir of antibodies in most individuals, the levels of which correlate with the extent of protection (93, 94). For example, higher pre-existing serum or nasal antibodies precluded RSV infections in the challenge studies (93, 95). Thus, immunity to RSV is the norm in the general adult population, since severe RSV infections are uncommon until advanced age (96, 97). Immunological considerations in the elderly are an important concern that we will discuss more in the next section. Thus, though it is clear that lifelong and complete protection against RSV from a single exposure is unlikely, the focus on only those individuals who rapidly lose protective antibody titers provides an incomplete picture of the typical response. As another example of an acute respiratory infection, studies of adults nearly 90 years after the 1918 influenza virus pandemic demonstrated high titers of serum neutralizing antibodies to the homologous strain (98). The remarkably durable immunity in individuals likely exposed as children probably arose from the primary response. At least for other vaccines, repeated stimulation of memory B cells is not required for serum antibody maintenance (52), demonstrating that primary infections and immunizations can confer durable antibody production. In further support of this interpretation, young children with no pre-existing immunity immunized with an MF59-adjuvanted influenza vaccine demonstrated robust and durable immunity (99). As a final example, homologous rhinovirus challenge studies demonstrated immunity for at least a year (100). Together, these data collectively demonstrate that durable protection against homotypic challenges following acute viral infections is the norm. Following natural infections with pathogens such as influenza viruses and rhinoviruses, the major factor imparting a loss of immunity is not short-lived antibody production, but rather the emergence of viral serotypes and genotypes that evade these defenses. Thus far, the rate of emergence of new genetic variants of SARS-CoV-2 has been slow (101), yet it is certainly possible that after widespread vaccination efforts and thus increased immune selective pressure, this rate will increase.

Immune responses in vulnerable populations against SARS-CoV-2 and against the potential COVID-19 vaccines

Though immunity following natural SARS-CoV-2 infection is likely to be durable, this is less clear for immunity to vaccines, especially given the experimental nature of many of these platforms (48, 102). These considerations are especially important when considering populations at special risk of severe disease and death from COVID-19. This includes those

over 60 (103), as well as persons with underlying medical conditions (diabetes, hypertension, chronic pulmonary diseases etc.), although by now it is very clear that SARS-CoV-2 can and will strike outside of these categories and that it can be fatal for young people with no underlying conditions at all. That fact highlights the limits of our knowledge and understanding of COVID-19 pathogenesis, an issue that would greatly benefit from a reliable animal model that recapitulates the main clinical findings from humans.

This issue notwithstanding, the questions on the immune responses in vulnerable populations, the durability of immunity in these populations and their protection by vaccination all remain at the forefront of both research and clinical medicine. Due to the space constraints, and due to the current state of knowledge, we will discuss these issues from the perspective of older adults, at the moment not considering the underlying conditions. It is worth noting that pronounced lymphopenia follows severe COVID-19 (104). Whether that reflects a lymphotoxic effect of SARS-CoV-2 or the SARS-CoV-2-modulated environment, or (more likely) redistribution of lymphocytes to target organs, such as the lung, or some other mechanism, remains to be seen. Usually, lymphopenia would bode ill for the immune responses in older adults, because older adults already lose substantial numbers of naïve CD8, and to a lesser extent CD4 and B cells (105, 106). Indeed, primary adaptive immune responses to new infections (T as well as B) in older adults are reduced, delayed and suboptimally coordinated (106). Interestingly, the literature so far has not supported such a common scenario in the case of SARS-CoV-2. Antibody responses in older adults were quantitatively robust and at least equivalent, if not superior to, those of their younger counterparts (15, 107), While the quality of these responses also appears comparable, this remains to be examined in greater detail with regard to affinity/avidity, repertoire breadth and functional capacity. Instead, it appears that the severity of infection seems to dictate the extent and intensity of the immune response (15, 107), which, by itself, does not correlate to the disease outcome. At the present, it appears that the coordination of the innate immune response may be key to successful containment of SARS-CoV-2 (108), and we have no information on whether or not this coordination may be adversely affected by the age of the subject.

Importantly, robust responses to SARS-CoV-2 in older adults give us hope that this population can be protected by both immunomodulation and vaccination. Vaccination in the elderly usually suffers from the same problems of other primary immune responses in the elderly, and is known to be efficacious in only half or even fewer of the individuals (17–51%, depending on the season), in the case of seasonal influenza vaccine, as compared to 70–85% in younger populations (109). However, new generation of vaccines, adjuvanted with patter recognition receptor (PRR) agonists, have been shown to induce highly efficient immune responses in older adults, with the varicella-zoster virus vaccine Shingrix®, conferring strong antibody immunity to >97% adults over 65 years of age (110). We therefore hold high hope that vaccine manufacturers will keep this in mind when designing SARS-CoV-2 vaccines, to protect broad swaths of vulnerable populations across the world.

Conclusions

The purpose of this article is not to paint an excessively rosy picture of the SARS-CoV-2/COVID-19 pandemic. Rather, the intent is to offer an objective perspective of antibody immunity. Doing so allows for a proper calibration of likelihoods, expectations, and uncertainty, thereby balancing particularly worrisome aspects of the virus to those that are of much lesser concern. There are many highly problematic immunopathological and epidemiological aspects of this virus, but we do not believe that subversion of fundamental immunological principles is among them.

Acknowledgments

Funding Sources

Funding was provided by the National Institutes of Health: R01AI099108 (D.B.), R01AI121252 (F.E.L.), R01AI117890 (N.B.) R01AI148652 (N.B.) and R37AG020719 (J.N.Z.).

Conflicts of interest

D.B. has intellectual property licensed by Sana Biotechnology. F.E.L. is a founder of MicroB-plex, Inc. and receives research funding from Genentech. J.N.Z. is on the scientific advisory board of and receives research funding from Young Blood Inc.

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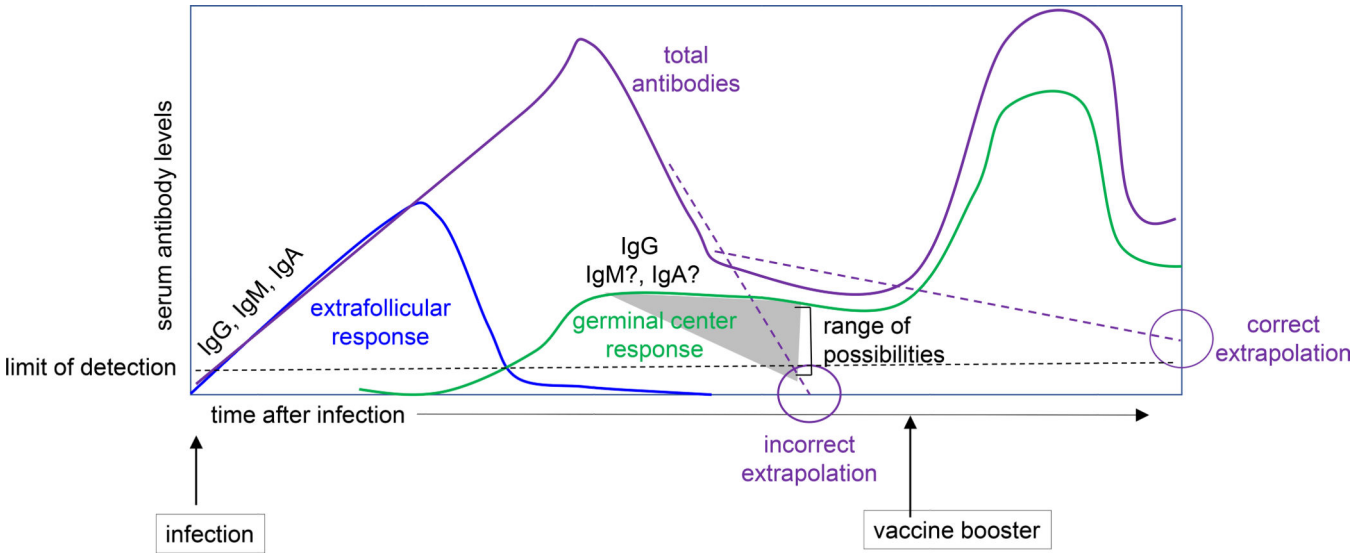

Figure 1: Kinetics of primary and secondary antibody responses against acute viral infections.

Early in the primary response, antibodies are contributed exclusively by extrafollicular plasmablasts and plasma cells (blue line). As the response progresses, germinal center-derived (green line) plasma cells with longer lifespans emerge and gradually increase in contribution to total antibody levels (purple line). Booster immunizations or re-infections trigger a memory B cell response, leading to a rapid rise in antibody levels through both germinal center-independent and -dependent mechanisms, and are often followed by a rapid decrease to levels just above pre-challenge concentrations.