Antibody Responses to SARS-CoV-2: Let’s Stick to Known Knowns

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The scale of the severe acute respiratory syndrome coronavirus 2 (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 Ab-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. *The Journal of Immunology, 2020, 205: 000–000.*

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has thrust immunology into the public spotlight in unprecedented ways, and discussions of Ab 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, 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 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 postinfection 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 and the World Health Organization (WHO), have made similar problematic “absence of evidence” statements regarding face masks, immunity postinfection, 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 Ab 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 naive. Although in this review we focus on humoral immunity with an emphasis on long-lived plasma cell (LLPC)-derived serum Abs, 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, whereas others circulate to patrol for distal exposures (6, 7). NK 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 reinfection 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. Although neither the KCDC, nor many scientists interviewed, considered it likely that these patients had been reinfected 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 reinfection 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 Abs prevented subsequent culture and community transmission. Second, the last PCR assay might have simply detected viral genomic remnants or noninfectious 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, whereas culturable virus was not retrievable, nor could virus transmission be detected (C. Yang, M. Jiang, X. Wang, X. Tang, S. Fang, H. Li, L. Zuo, Y. Jiang, Y. Zhong, Q. Chen, et al., manuscript posted on medRxiv, DOI: 10.1101/2020.07.21.20125138).

**Immunity and resistance to reinfection.** Concomitantly, several groups reported clear evidence of immunity after SARS-CoV-2 infection and clearance. Seroconversion and neutralizing Ab production, which is the best correlate of protection for many infections and almost all vaccines (13), were observed in nearly all convalescent patients with confirmed COVID-19 (14). For most acute viral infections and following vaccination, the presence of neutralizing Abs is a clear functional correlate of immunity (13) 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 (15, 16). Although 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 (Ref. 17 and S. T. H. Liu, H.-M. Lin, I. Baine, A. Wajnberg, J. P. Gunprecht, F. Rahman, D. Rodriguez, P. Tandon, A. Bassily-Marcus, J. Bander, et al., manuscript posted on medRxiv, DOI: 10.1101/2020.05.20.20102236).

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 rechallenge with SARS-CoV-2 (Ref. 18 and L. Bao, W. Deng, H. Gao, C. Xiao, J. Liu, J. Xue, Q. Lv, J. Liu, P. Yu, Y. Xu, et al., manuscript posted on bioRxiv, DOI: 10.1101/2020.03.13.990226). 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 postinfection, at least to certain viral Ags, 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, as has been reported in several recent anecdotal cases. However, the percentages of individuals not seroconverting (claimed by some studies) seem unlikely, ranging from 10 to 80% (Ref. 19 and T. Sekine, A. Perez-Potti, O. Rivera-Ballesteros, K. Strälin, J.-B. Gorin, A. Olsson, S. Llewellyn-Lacey, H. Kamal, G. Bogdanovic, S. Muschiol, et al., manuscript posted on bioRxiv, DOI: 10.1101/2020.06.29.174888; T. Liu, S. Wu, H. Tao, G. Zeng, F. Zhou, F. Guo, and X. Wang, manuscript posted on medRxiv, DOI: 10.1101/2020.06.13.20130252), 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 (14, 20–23). Given the evidence, a statement of, “It is unlikely that COVID-19–infected patients who develop antibodies can be reinfected,” would have conveyed a message of assurance rather than hysteria and would have been entirely consistent with the accumulated evidence.

Challenges with Ab testing and data interpretation for SARS-CoV2. Although the original WHO statement on Abs and reinfection was off target in our opinion, a legitimate concern is the degree to which a positive Ab 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, a mechanism employed to allow products to be sold under emergency use authorizations by the Food and Drug Administration, 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 was unreliable, with poor specificity and sensitivity compared with conventional ELISAs (J. D. Whitman, J. Hiatt, C. T. Mowery, B. R. Shy, R. Yu, T. N. Yamamoto, U. Rathore, G. M. Goldgof, C. Whitty, J. M. Woo, et al., manuscript posted on medRxiv, DOI: 10.1101/2020.04.25.20074856). The Food and Drug Administration has subsequently removed many of these products in the United States. 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 (21, 22, 24). Such doubt has been amplified in the news media and risks depriving infectious disease epidemiologists of a valuable tool in monitoring community transmission as well as physicians treating COVID-19 subjects of convalescent plasma, proven to contain protective anti–SARS-CoV-2 Abs.

One of the intended uses of many of the point-of-care tests was to distinguish the timing of infection based on Ab isotype. As primary B cell responses often begin with secretion of IgM, it was assumed that production of this Ab 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 Ab responses to infections shape the serum Ab 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 Ags. B cell plasmablasts develop rapidly following an acute infection, and these responses provide much of the earliest measurable wave of serum Abs. 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 (Fig. 1). Respiratory tract infections induce IgM, IgG, and IgA, as indeed found for patients infected with SARS-CoV-2 (Refs. 14, 25, and M. Woodruff, R. Ramonell, K. Cashman, D. Nguyen, A. Saini, N. Haddad, A. Ley, S. Kyu, J. C. Howell, T. Ozturk, et al., manuscript posted on medRxiv, DOI: 10.1101/2020.04.29.20083717). Based on current understanding of these mostly T-dependent responses, there is no expectation that IgM responses necessarily precede class-switched responses, as class-switching is rapidly induced during the process of B cell activation and clonal expansion (26–28) 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” (27), 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 nonswitched IgM memory B cells (29) and may even lead to long-lived IgM responses by plasma cells secreting IgM for extended periods of time (30, 31), 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 LLPCs 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 Abs, such as IgG and IgA.
Because the half-life of IgM is only in the order of a few days (32) in contrast to that of IgG, which is in the order of 3–4 wk 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 (Refs. 14, 25, and M. Woodruff, et al., manuscript posted on medRxiv, DOI: 10.1101/2020.04.29.20083717). 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 (M. Woodruff, et al., manuscript posted on medRxiv, DOI: 10.1101/2020.04.29.20083717). 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 Abs, both switched and nonswitched. Asymptomatic patients and those with mild disease exhibit lower overall Ab responses but do also possess neutralizing titers (33–35). As convalescence begins, B cell responses shift from “emergency supply” to the development of long-lived responses in germinal center responses, which are geared toward 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 (J. H. Lam and N. Baumgarth, manuscript in preparation).

Within the germinal center reaction, B cells undergo somatic hypermutation of their Ig genes and selection for those variants with higher affinity for Ag. High-affinity variants are then fated for either memory B or plasma cell differentiation. Generally, as Ab affinity increases over time, so too does the lifespan and secretory capacity of plasma cells (36–38). Consequently, relatively few plasma cells are required to confer protection against subsequent infections, provided Abs 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 three Ag-specific LLPCs, is enough to protect a naive mouse from an otherwise lethal inoculum (39). Plasma cell lifespan is variable based on the specific vaccine or infection, but as a general rule, the duration of Ab production is very long after natural exposures, as seen in responses to acute viruses such as mumps and measles (40). LLPCs are the sources of this durable Ab production (41–46). Humoral immunity to chronic infections such as those caused by HIV and human papillomavirus, where viral Ags can persist in the host, are more complex (47). Given the acute nature of SARS-CoV-2 infections, chronic infections will not be discussed further in this article.

**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, whereas IgG titers should wane slower and remain elevated for extended periods of time (B. Borremans, A. Gamble, K. C. Prager, S. K. Helman, A. M. McClain, C. Cox, V. Savage, and J. O. Lloyd-Smith, manuscript posted on medRxiv, DOI: 10.1101/2020.05.15.20103275). 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 (48). As demonstrated by the highly successful i.m. human papillomavirus vaccine, IgG can protect against mucosal infections through a combination of transcytosis and transudation (49). Second, serum IgA is usually monomeric rather than dimeric (50) 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 (51). Thus, the rapid waning of IgA responses observed in COVID-19 patients (M. Woodruff, et al., manuscript posted on medRxiv, DOI: 10.1101/2020.04.29.20083717; A. S. Iyer, F. K. Jones, A. Nodoushania, M. Kelly, M. Becker, D. Slater, R. Mills, E. Teng, M. Kamruzzaman, W. F. Garcia-Beltran, et al., manuscript posted on medRxiv,
may be unable to support germinal center responses. With ongoing dysregulated inflammatory responses may not be captured by serological testing. Critically ill individuals Ab and/or cell-mediated immunity (7, 52), which would not in the upper respiratory tract may develop local tissue-resident humoral immunity that can be expected to last for extended periods of time. Patients with only mild and localized infection with homologous viruses such as SARS-CoV-2, fall within the latter, so too do less dangerous strains such as Middle East respiratory syndrome, SARS-CoV-1, and including Middle East respiratory syndrome, SARS-CoV-1, and SARS-CoV-2, fall within the latter, so too do less dangerous and more common strains, including OC43 and HKU1 (64).

Why, then, do we keep getting infected with common coronaviruses so often (Ref. 70 and A. T. Huang, B. Garcia-Carreras, M. D. T. Hitchings, B. Yang, L. Katzelnick, S. M. Rattigan, B. Borgert, C. Moreno, B. D. Solomon, I. Rodriguez-Barraquer, et al., manuscript posted on medRxiv, DOI: 10.1101/2020.04.14.20065771)? The answer may lie on the unappreciated genetic diversity of coronavirus strains (71–73). The mutation rate for both SARS-CoV-2 and common coronaviruses is relatively low (for NL63, the estimated substitution rate is \(3 \times 10^{-4}\) per site per year in the spike protein), but some of the common coronaviruses have been circulating among the human population for an estimated 1000 y (Ref. 71 and J. T. Ladner, B. B. Larsen, J. R. Bowers, C. M. Hepp, E. Bolyen, M. Folkerts, K. Sheridan, A. Pfeiffer, H. Yaglom, D. Lemmer, et al., manuscript posted on medRxiv, DOI: 10.1101/2020.05.08.20095935). 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 (68). The extent to which prior coronavirus
infections impact heterologous immunity to SARS-CoV-2 remains under investigation (Ref. 20 and T. Sekine, et al., manuscript posted on bioRxiv, DOI: 10.1101/2020.06.29.174888; and K. Ng, N. Faulkner, G. Cornish, A. Rosa, C. Earl, A. Wrobel, D. Benton, C. Roustan, W. Bolland, R. Thompson, et al., manuscript posted on bioRxiv, DOI: 10.1101/2020.05.14.095414).

Duration of immunity to SARS-CoV-1 and SARS-CoV-2. Intentional challenge studies are of course not ethical for deadly strains such as Middle East respiratory syndrome 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 Ab titers peaked at month 4 and their geometric mean reciprocal titers declined 7-fold and 10-fold at months 24 and 36, respectively (74). Based on these data, it was concluded that Ab production lasts for only 1–3 y 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 Abs. For most acute challenges, a relatively stable nadir is eventually achieved of Abs continuously produced by LLPCs (41). Thus, the decay of Ab 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 (Fig. 1). Indeed, recent studies reported that SARS-CoV-1–neutralizing Abs could still be detected 12–17 y after the infection was resolved (Ref. 75 and X. Guo, Z. Guo, C. Duan, Z. Chen, G. Wang, Y. Lu, M. Li, and J. Lu, manuscript posted on medRxiv, DOI: 10.1101/2020.02.12.200021386). Interestingly, Ab titers were low as measured by standard ELISAs, demonstrating that very small quantities of high-affinity Abs 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 reinfection 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 Ab responses against the nucleocapsid protein, especially those in who recovered from mildly symptomatic disease (Ref. 33 and J. Seow, C. Graham, B. Merrick, S. Acors, K. A. Steel, O. Hemmings, A. O’ Byrne, N. Koupouh, S. Pickering, R. Galao, et al., manuscript posted on medRxiv, DOI: 10.1101/2020.07.09.20148429). For the same reasons as discussed above for SARS-CoV-1, such conclusions are premature in our view. All Ab 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 (40). Moreover, neutralizing Abs to SARS-CoV-2, which presumably bind the spike protein, remained very high in the same study (33). The discrepancy might reflect differences in either assay sensitivity or Ab responses to nucleocapsid versus 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 Ab 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 Abs as well as cellular measures that include circulating and tissue-resident memory T and B cells.

Durability of Ab 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. Postinfection, neutralizing Abs do indeed decline initially (76), as is seen in all humoral responses irrespective of the ultimate duration of immunity (40). 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 Abs in most individuals, the levels of which correlate with the extent of protection (77, 78). For example, higher pre-existing serum or nasal Abs precluded RSV infections in the challenge studies (77, 79). Thus, immunity to RSV is the norm in the general adult population because severe RSV infections are uncommon until advanced age (80, 81). Immunological considerations in the elderly are an important concern that we will discuss more in the next section. Thus, although it is clear that life-long and complete protection against RSV from a single exposure is unlikely, the focus on only those individuals who rapidly lose protective Ab titers provides an incomplete picture of the typical response. As another example of an acute respiratory infection, studies of adults nearly 90 y after the 1918 influenza virus pandemic demonstrated high titers of serum neutralizing Abs to the homologous strain (82). 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 Ab maintenance (44), demonstrating that primary infections and immunizations can confer durable Ab 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 (83). As a final example, homologous rhinovirus challenge studies demonstrated immunity for at least a year (84). 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 Ab 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 (J. T. Ladner, et al., manuscript posted on medRxiv, DOI: 10.1101/2020.05.08.20095935), 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"

Although 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 (Ref. 40 and M. J. Mulligan, K. E. Lyke,
N. Kitchin, J. Absalon, A. Gurtman, S. P. Lockhart, K. Neuzil, V. Raabe, R. Bailey, K. A. Swanson, et al., manuscript posted on medRxiv, DOI: 10.1101/2020.06.30.20142570. These considerations are especially important when considering populations at special risk of severe disease and death from COVID-19. This includes those over 60 (85) 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. Because of the space constraints, and 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 (D. Mathew, J. R. Giles, A. E. Baxter, A. R. Greenplate, J. E. Wu, C. Alanio, D. A. Oldridge, L. Kuri-Cervantes, M. B. Pampena, K. D’Andrea, et al., manuscript posted on bioRxiv, DOI: 10.1101/2020.05.20.106401). 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 naive CD8 and to a lesser extent CD4 and B cells (86, 87). Indeed, primary adaptive immune responses to new infections (T as well as B) in older adults are reduced, delayed, and suboptimally coordinated (87). Interestingly, the literature so far has not supported such a common scenario in the case of SARS-CoV-2. AB responses in older adults were quantitatively robust and at least equivalent, if not superior to, those of their younger counterparts (14, 88). Although 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 (14, 88), 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 (89), and we have no information on whether 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 with 70–85% in younger populations (90). However, new generation of vaccines, adjuvanted with pattern 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 Ab immunity to >97% adults over 65 y of age (91). 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 Ab immunity. Doing so allows for a proper calibration of likelihoods, expectations, and uncertainty, thereby balancing particularly worrisome aspects of the virus with those that are of much less 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.

Disclosures

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