COMMENTARY

American Journal of Human Biology **WILEY**

Beyond serosurveys: Human biology and the measurement of SARS-Cov-2 antibodies

Thomas W. McDade[1,2] | **Amelia Sancilio**[1,3]

[1]Department of Anthropology, Northwestern University, Evanston, Illinois

[2]Institute for Policy Research, Northwestern University, Evanston, Illinois

[3]Center for Health and the Social Sciences, University of Chicago, Chicago, Illinois

Correspondence
Thomas W. McDade, Department of Anthropology, Northwestern University Evanston, Il.
Email: t-mcdade@northwestern.edu

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) has emerged as a deadly clinical disease. The virus that causes COVID-19, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is readily transmitted in the community, where it is having devastating social and economic impacts. Yet our understanding of SARS and COVID-19 is derived primarily from studying the most severe cases in clinical and hospital settings. A complementary, field-based approach is desperately needed, and human biologists are well-positioned to make important contributions to our understanding of which individuals, and communities, are most vulnerable and why.

Much has been said about shortcomings in the roll out ofSARS-CoV-2 testing and how it has frustrated efforts to identify cases and isolate individuals who are shedding virus. Less has been said about the opportunities that testing provides for a wide range of research applications. In this commentary, we describe antibody testing and how human biologists can use it to inform our understanding of the pandemic, and to address questions of longstanding interest regarding the causes and consequences of human biological variation.

2 | TESTING FOR SARS-COV-2: CURRENT AND PRIOR EXPOSURE

Nucleic acid-based (ie, polymerase chain reaction, PCR) tests of naso-pharyngeal swabs and/or saliva can detect the presence of virus in the acute stage of infection. These tests are important for clinical diagnosis, and if deployed more widely can be used to identify viral spread in the community. However, shortages of swabs, personal protective equipment (PPE), transport media, and accurate testing platforms have led to a rationing of tests. As a result, priority has been given to testing suspected cases of COVID-19, with limited application outside the clinical context through the first wave of the pandemic. It is also becoming apparent that false negative results may be more common than originally thought, as viral RNA production in the naso-pharynx is transient and subject to sampling variability.

Serological testing is a complementary approach that detects the presence of antibodies against SARS-CoV-2 in blood samples from exposed individuals (World Health Organization, 2020). As the immune system mounts a response to infection, B lymphocytes produce antibodies against viral proteins which bind, and in some cases, neutralize the virus. The isotype immunoglobulin M (IgM) is the first antibody to appear in circulation following initial exposure to an antigen. It is a large pentamer that is detectable 3 to 10 days after infection, but its expression is transient and concentrations decrease in the weeks following exposure (Zhao et al., 2020). IgG production is slower to come online, but antibodies of this isotype remain detectable for months, and often years, after infection (Tan et al., 2020; Xiao, Gao, & Zhang, 2020).

Based on these dynamics, antibody testing can be applied clinically to diagnose a current or very recent infection, and epidemiologically as a surveillance tool. For example, in some cases individuals present with symptoms of COVID-19 but test negative with PCR because the

virus has been cleared, viral shedding is not occurring at the time of sampling, and/or technical errors lead to a false negative result. If sufficient time has passed since the initial infection, the presence of IgM antibodies against SARS-CoV-2 antigens can be used to confirm a clinical case of COVID-19. The time course of IgG production makes testing less relevant for diagnosis of acute infection, but since levels of anti-SARS IgG antibodies remain elevated long after infection, IgG testing can be used to identify "cases" after the fact. As described below, there are several ways these tests can inform research and policy related to COVID-19.

There are currently two predominant approaches to antibody testing: enzyme linked immunosorbent assay (ELISA), and lateral flow immunoassay (LFIA). In ELISA, viral antigen is fixed to the bottom of a microtiter plate well, diluted serum or plasma is added, and antibodies specific to the viral antigen, if present, are "captured" in the well. The addition of anti-human IgG or IgM antibody with a label (eg, horseradish peroxidase) generates a signal proportional to the concentration of captured antibody, which is quantified in a spectrophotometer. ELISA protocols for SARS-CoV-2 IgM and IgG antibodies for use with serum or plasma are now established (Amanat et al., 2020).

However, the requirement for serum/plasma is a significant constraint, particularly in the context of the current pandemic. Under the best of circumstances, venipuncture is difficult to implement outside the clinical setting due to the logistics of drawing, transporting, and processing venous blood. These challenges are compounded when people are told to stay at home, and when phlebotomists and PPE are in short supply because cases of COVID-19 are surging.

Lateral flow immunoassay tests have the potential to overcome these obstacles in that they typically require only a few drops of capillary whole blood, collected from a simple finger stick. As such, they can be readily implemented in nonclinical, community-based settings with the potential to reach larger numbers of people. In LFIA, the antigen-antibody dynamics of ELISA are applied in a cartridge format: Blood (and often diluent) is placed in a small well, and as it diffuses through the cartridge antibodies are labeled and captured, with a test line emerging to indicate a positive result. An advantage of LFIA is that it is a "point-of-care" test, with results available in 5 to 10 minutes. However, these tests are qualitative rather than quantitative, and even though they use only a few drops of finger stick blood, they are difficult to self-administer and usually require a trained health care worker to implement. In addition, recent analyses have raised substantial concerns regarding the accuracy of LFIA tests for SARS-CoV-2 IgG antibodies (Adams et al., 2020).

There is a middle ground in dried blood spot (DBS) sampling, which combines the convenience of blood collection in the community with the quantification that is possible in the lab (McDade, 2014; McDade, Williams, & Snodgrass, 2007). A sterile lancet is used to prick the finger, and up to five drops of whole blood are collected on filter paper. Once the sample dries, the cards can be closed, stacked, and transported to the lab without a cold chain. Most analytes remain stable in DBS for days, if not weeks or months, providing flexibility in blood collection protocols.

Human biologists are accustomed to conducting research outside the clinic or lab, and DBS sampling has been an important part of our toolkit for more than 25 years (Worthman & Stallings, 1997). Recently, we validated an ELISA for SARS-CoV-2 IgG antibodies in DBS that provides results that correlate highly with serum (R = 0.99) (McDade et al., 2020). The DBS approach has several advantages that make it particularly well-suited to address important gaps in the current COVID-19 testing landscape. First, individuals can self-sample in the home. Although some samples may be inadequate for analysis, prior applications have demonstrated the feasibility of having, participants collect their own DBS sample (Roberts et al., 2016). Second, samples can be returned in the mail without special handling (the CDC and US Postal Service consider DBS specimens nonregulated, exempt materials) (Centers for Disease Control and Prevention, 2017). Third, since DBS samples are analyzed in the lab, we can apply more accurate and quantitative protocols than is possible with LFIA. In developing a low-cost ELISA for SARS-CoV-2 antibodies, our hope is that others can draw on the longstanding tradition of methodological innovation in human biology to promote community-based research on COVID-19.

3 | UNANSWERED QUESTIONS AND THE POTENTIAL CONTRIBUTION OF HUMAN BIOLOGISTS

The burden of COVID-19 is not shared equally. For example, older persons are at higher risk for more serious complications and death, while rates of infection appear low for children and risk of mortality is even lower (Center for Disease Control and Prevention, 2020). Worldwide, minority and vulnerable populations have been disproportionately impacted by the COVID-19 pandemic. In the UK, though people from ethnic minorities are younger on average than the white British population, death rates are higher (Kirby, 2020). In the US, African Americans comprise 33% of COVID-19 hospitalizations (Kirby, 2020). In

the city of Chicago, as of June 1 the infection rate for Latinx residents was 2102 cases per 100 000, compared with 575 per 100 000 white residents. Mortality risk of COVID-19 was 2.6 times higher for African-Americans in comparison with whites (Chicago Department of Public Health, 2020).

Of course, these data paint an incomplete picture of the actual distribution of the virus since they are based on PCR tests for active infections in clinical settings. By identifying mild and asymptomatic cases, antibody testing can provide a more accurate and comprehensive record of the social and geographic spread of the virus. These data are important for informing estimates of the seroprevalence of infection and case fatality rates, for identifying subgroups of individuals more susceptible to infection, and for evaluating the effectiveness of various policy efforts (eg, social distancing, closing of schools and businesses) in mitigating transmission in the community. These are important first order questions, the answers to which can be used to inform public health responses to future outbreaks.

As human biologists we can contribute to this effort, but we can also dig deeper. We can complement the public health emphasis on surveillance, and the clinical emphasis on diagnosis and treatment, with research that illuminates the contextual, interpersonal, and individual factors that explain patterns of exposure and response to infection. We can draw on biosocial/biocultural frameworks to develop a more holistic picture of individual variation in vulnerability to infection by integrating biological, sociocultural, and environmental data. A key strength of this perspective is the emphasis on simultaneously defining and measuring causal pathways at multiple levels, which can highlight proximate as well as more distal causes of inequities in exposure, infection, and death.

For example, are higher rates of COVID-19 mortality among African-Americans a product of increased exposure to SARS-CoV-2, or increased vulnerability to disease following exposure? Not everyone is afforded the same opportunity to shelter-in-place. Workers designated as "essential," and those who cannot afford to stay home even when rates of community transmission are high, are at increased risk for exposure (as are the other members of their household and social networks). Furthermore, food deserts, inadequate health care, limited opportunities for physical activity, and stress all contribute to hypertension and diabetes—conditions that predispose to COVID-19 mortality. As discrimination, concentrated disadvantage, and other forms of structural racism increase burdens of chronic degenerative disease among African-Americans in the US, they may also contribute to inequities in COVID-19 mortality. Antibody testing can be used to cast light on the inequitable distribution of viral exposure and the factors that contribute to higher levels of transmission in disadvantaged communities.

Human biologists are also well-positioned to consider a life course perspective on variation in outcomes in response to SARS-CoV-2 infection. Why are older people more vulnerable, while children are largely spared? Why do infections tend to be mild in pregnancy, in contrast to the 1918 influenza pandemic when mortality was particularly high for pregnant women (Taubenberger & Morens, 2006)? Developmental plasticity, ecological sensitivity, and the finite nature of resources are key concepts from evolutionary life history theory that may generate important insights. For example, the immune system is a central component of maintenance effort, and the defenses that provide protection against COVID-19 are costly to develop and activate (McDade, 2003). One might therefore hypothesize that the response to infection is shaped by the availability of nutritional resources, particularly resources during sensitive periods of immune development in infancy. Similarly, microbial exposures early in development may calibrate investments in innate vs specific immunity, with implications for the regulation—or dysregulation—of inflammation in adulthood (McDade, Georgiev, & Kuzawa, 2016). A theoretically grounded, hypothesis driven life history approach may help us identify how, and why, individuals differ in the magnitude and effectiveness of immune responsiveness to SARS-CoV-2 infection. Quantifying the antibody response to infection provides a direct measure of humoral immunity, and additional indicators of immune activity (eg, markers of inflammation, cell mediated responses) can further characterize the magnitude and direction of response.

We can also reach across generations to consider the potential long-term implications of the pandemic. Even though pregnant women do not appear to be at elevated risk of infection, subtle long term effects on individuals born during the 1918 influenza epidemic are well-documented (Almond, 2006), and recent research showing how maternal adversity can shape placental architecture and nutrient transfer point toward the possibility of intergenerational impacts of infection (Miller et al., 2017). In addition, it is not just mothers that we should consider: The experience of fathers may be transmitted across generations as well, through epigenetic modifications to the germline that are inherited along with gene sequence (Ryan & Kuzawa, 2020). We can also reach back in time, to consider how adaptations to environmental pressures may influence responses to infection in the present. For example, recent research with high-altitude populations in regions of Tibet, Bolivia, and Ecuador suggests that physiological responses that promote survival in hypoxic environments may also serve to

decrease susceptibility to SARS-CoV-2 infection (Arias-Reyes et al., 2020). These are all questions that can be answered, at least in part, with measures of antibody response to identity individuals who have been exposed.

4 | CONCLUSION

Human biologists are uniquely positioned to make important contributions to our understanding of COVID-19, and methods that facilitate research in community-based settings globally will be central to that effort. Antibody testing is a necessary surveillance tool, but we can also apply it in the service of advancing our understanding of human biological variation more broadly. In doing so we accept an obligation to challenge misleading claims regarding the significance of a "positive" antibody test. At this point it is not known if high levels of SARS-CoV-2 IgG antibodies confer immunity against future infection, and talk of antibody badges or passports is premature. We also need to be mindful of the potential for seroprevalence data to stigmatize members of the community, and to politicize debates regarding the costs and benefits of initiatives designed to mitigate viral transmission. The current pandemic underscores the social nature of human biology, and a contextualized, community-based approach is an essential complement to current clinical and public health research paradigms.

AUTHOR CONTRIBUTIONS

Thomas W. McDade: Conceptualization; writing-original draft; writing-review and editing. **Amelia Sancilio:** Writing-original draft; writing-review and editing.

ORCID

Thomas W. McDade https://orcid.org/0000-0001-5829-648X

Amelia Sancilio https://orcid.org/0000-0002-4823-3829

REFERENCES

Almond, D. (2006). Is the 1918 influenza pandemic over? Long-term effects of in utero influenza exposure in the post-1940 U.S. population. *Journal of Political Economy*, *114*(4), 672–712.

Amanat, F., Stadlbauer, D., Strohmeier, S., Nguyen, T. H., Chromikova, V., McMahon, M., ... Bermudez-Gonzalez, M. (2020). A serological assay to detect SARS-CoV-2 seroconversion in humans. Nature Medicine, 1–4. Adams, E. R., Anand, R., Andersson, M. I., Auckland, K., Baillie, J. K., Barnes, E., ... Carroll, M. (2020). Evaluation of antibody testing for SARS-Cov-2 using ELISA and lateral flow immunoassays. *medRxiv*. https://doi.org/10.1101/2020.04.15.20066407

Arias-Reyes, C., Zubieta-DeUrioste, N., Poma-Machicao, L., Aliaga-Raudan, F., Carvajal-Rodriguez, F., Dutschmann, M., ... Soliz, J. (2020). Does the pathogenesis of SAR-CoV-2 virus

decrease at high-altitude? *Respiratory Physiology & Neurobiology*, 103443.

Centers for Disease Control and Prevention (2017). Shipping guidelines for dried-blood spot specimens. Retrieved from https://www.cdc.gov/labstandards/pdf/nsqap/Bloodspot_Transportation_Guidelines.pdf

Centers for Disease Control and Prevention (2020). Older Adults. Retrieved from https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/older-adults.html

Chicago Department of Public Health (2020). *Latest Data*. Chicago, IL: City of Chicago. Retrieved from https://www.chicago.gov/city/en/sites/covid-19/home/latest-data.html.

Kirby, T. (2020). Evidence mounts on the disproportionate effect of COVID-19 on ethnic minorities. *The Lancet Respiratory Medicine*, *8*, 547–548.

McDade, T. (2003). Life history theory and the immune system: Steps toward a human ecological immunology. *Yearbook of Physical Anthropology*, *4*, 100–125.

McDade, T. W. (2014). Development and validation of assay protocols for use with dried blood spot samples. *American Journal of Human Biology*, *26*(1), 1–9. https://doi.org/10.1002/ajhb.22463

McDade, T. W., Georgiev, A. V., & Kuzawa, C. W. (2016). Trade-offs between acquired and innate immune defenses in humans. *Evol Med Public Health*, *2016*(1), 1–16. https://doi.org/10.1093/emph/eov033

McDade, T. W., McNally, E., D'Aquila, R. T., Mustanski, B., Miller, A., Vaught, L., ... Demonbreun, A. (2020). Enzyme immunoassay for SARS-CoV-2 antibodies in dried blood spot samples: A minimally-invasive approach to facilitate community-and population-based screening. *medRxiv*. Retrieved from https://doi.org/10.1101/2020.04.28.20081844

McDade, T. W., Williams, S., & Snodgrass, J. J. (2007). What a drop can do: Dried blood spots as a minimally invasive method for integrating biomarkers into population-based research. *Demography*, *44*(4), 899–925.

Miller, G. E., Culhane, J., Grobman, W., Simhan, H., Williamson, D. E., Adam, E. K., ... Borders, A. (2017). Mothers' childhood hardship forecasts adverse pregnancy outcomes: Role of inflammatory, lifestyle, and psychosocial pathways. *Brain, Behavior, and Immunity*, *65*, 11–19. https://doi.org/10.1016/j.bbi.2017.04.018

Roberts, S. C., Seav, S. M., McDade, T. W., Dominick, S. A., Gorman, J. R., Whitcomb, B. W., & Su, H. I. (2016). Self-collected dried blood spots as a tool for measuring ovarian reserve in young female cancer survivors. *Human Reproduction*, *31*(7), 1570–1578. https://doi.org/10.1093/humrep/dew114

Ryan, C. P., & Kuzawa, C. W. (2020). Germline epigenetic inheritance: Challenges and opportunities for linking human paternal experience with offspring biology and health. *Evolutionary Anthropology*. https://doi.org/10.1002/evan.21828

Tan, W., Lu, Y., Zhang, J., Wang, J., Dan, Y., Tan, Z., . . . Hu, Q. (2020). Viral kinetics and antibody responses in patients with COVID-19. *medRxiv*. https://doi.org/10.1101/2020.03.24.20042382.

Taubenberger, J. K., & Morens, D. M. (2006). 1918 influenza: The mother of all pandemics. *Revista Biomedica*, *17*(1), 69–79.

World Health Organization (2020). Population-based age-stratified seroepidemiological investigation protocol for COVID-19 virus infection, march 17, 2020.

Worthman, C. M., & Stallings, J. F. (1997). Hormone measures in finger-prick blood spot samples: New field methods for reproductive endocrinology. *American Journal of Physical Anthropology: The Official Publication of the American Association of Physical Anthropologists*, *104*(1), 1–21.

Xiao, A. T., Gao, C., & Zhang, S. (2020). Profile of specific antibodies to SARS-CoV-2: The first report. *The Journal of Infection*, *8*(1), 147–178.

Zhao, J., Yuan, Q., Wang, H., Liu, W., Liao, X., Su, Y., … Li, J. (2020). Antibody responses to SARS-CoV-2 in patients of novel coronavirus disease 2019. *Clinical Infectious Diseases*, ciaa344. https://doi.org/10.1093/cid/ciaa344