



Refocusing the Conduct of Maternal Mortality Research in Black Pregnant Populations

Ethical Considerations

Alexis Dunn Amore, PhD, CNM, FACNM, FAAN

ABSTRACT

Introduction: Maternal morbidity and mortality rates are on the rise in the United States, particularly among Black populations. Recently, there has been an uptick in research funding to identify and address root causes, particularly among at-risk groups. However, given the historical trauma experienced by Black populations in research settings, novel approaches built firmly on ethical principles and grounded in a framework of reproductive justice are necessary to minimize harm and center the research process on maintaining the dignity and respect of research participants.

Methods: Ethical principles as outlined by the American Nurses Association, Black Mamas Matter Alliance, and federal research guidelines are reviewed within the context

of conducting maternal mortality-focused research. In addition, community developed research frameworks and methodologies are presented and discussed within the research context. **Conclusions:** Black pregnant people have reported mistreatment during clinical encounters; therefore, intentional protections to promote safety must be considered in the research setting. Ethical principles must be considered when designing and implementing research initiatives focused on addressing maternal mortality risk in Black communities.

Key Words: community-based participatory research, maternal morbidity, maternal mortality, reproductive justice, research ethics

Author Affiliation: Nell Hodgson Woodruff School of Nursing, Emory University, Atlanta, Georgia.

Dr Amore is currently funded on a project supported by the National Center for Advancing Translational Sciences (NCATS) of the National Institutes of Health (NIH) under Award nos. UL1TR002378 and 1R01NR019254. She is also funded with the Emory Robert W. Woodruff Health Sciences Fund, Emory University.

The content of this article is solely the responsibility of the author and does not necessarily represent the official views of the National Institutes of Health or Emory University.

Disclosure: The author has disclosed that she has no significant relationships with, or financial interest in, any commercial companies pertaining to this article.

Each author has indicated that he or she has met the journal's requirements for Authorship.

Corresponding Author: Alexis Dunn Amore, PhD, CNM, FACNM, FAAN, Nell Hodgson Woodruff School of Nursing, Emory University, 1520 Clifton Rd, NE, Atlanta, GA 30322 (alexis.dunn.amore@emory.edu).

Submitted for publication: November 15, 2021; accepted for publication: January 28, 2022.

There is a rising trend in the rates of maternal mortality in the United States compared with other high-income countries where rates are on the decline.¹ According to the 2019 report from the National Center for Vital Statistics, the United States continues to grapple with an increasing maternal mortality rate (MMR). The MMR in 2019 was 20.1 deaths per 100 000 live births, which increased from the rate in 2018 of 17.4 deaths per 100 000 live births.² Even more alarming are the disparities in risk among various populations. Black people in the United States are most at risk for dying (mortality) or becoming severely ill (morbidity) during the perinatal period, with an MMR of 44.0 deaths per 100 000 live births compared with non-Hispanic White (17.9) and Hispanic (12.6) populations.² Recently, there has been an uptick in research funding to identify and eliminate the root causes of maternal morbidity and mortality across all groups, as well as research calls

focused on developing and identifying community-based initiatives in Black populations of pregnant people. In response, there has been an increased interest in investigating the leading contributors to the crisis as well as efforts to implement novel approaches among populations at greatest risk.

Historically, there have been major ethical breaches in research involving Black populations.³⁻⁵ As such, Black populations are more likely to report concerns of trauma, distrust, and hesitancy when it comes to participating in research initiatives.^{3,5} Coupled with the twin pandemics of racism and health disparities exacerbated by COVID-19,^{6,7} Black populations are facing a unique set of circumstances in the present health-care climate. The complexity of this experience must be carefully considered before an onslaught of studies and initiatives are developed and haphazardly thrust upon the community. Strategies that are built firmly on ethical principles, designed by scholars of color, and grounded with the voices of community stakeholders are necessary to address poor outcomes and improve the experiences of Black people who engage in research initiatives.

The purpose of this article is to (1) review examples of ethical principles to consider when designing and implementing research initiatives focused on addressing maternal mortality risk in Black communities; (2) discuss examples of community developed research frameworks and methodologies that may be useful when designing and implementing studies; and (3) discuss the role of the nursing profession in leading ethically driven research initiatives.

ETHICAL PRINCIPLES

Ethical principles: General concepts

Ethics is a branch of philosophy that encompasses a variety of concepts related to moral principles that influence how individuals make decisions.⁸ These concepts are complex and vary among individuals, as many ethical concepts are derived from religion, philosophy, and culture. As such, many disciplines, including nursing, set standards of conduct to govern activities within a profession and to outline professional commitment to the larger society.⁹ The nursing code of ethics from the American Nurses Association outlines key elements (eg, benevolence, beneficence, respect, nonmaleficence, fidelity, accountability, veracity, patient autonomy) written into 9 provisions to guide the profession in a variety of settings including educational accreditation, certification and licensure, nursing practice, and research.⁹

Ethical principles are the foundation of federal guidelines overseeing the protection of human sub-

jects in research.¹⁰ The goal is to minimize harm, maximize benefits, and promote the respect, dignity, and autonomy of research participants.^{8,10} In addition, the guidelines outline considerations related to ethical aspects of the research design, methods, and procedures to ensure that research endeavors are completed with scientific integrity.¹⁰ Institutional review boards oversee the review process for research grants and ensure that research proposals are appropriate; however, use of these guiding principles early in the research process will ensure that proposed initiatives are credible and effective for the populations under investigation.

Ethical principles: Maternal mortality research

Ethical principles to consider when developing research initiatives focused on addressing health disparities in Black populations may best be evaluated from a lens of reproductive justice, a human rights lens that centers bodily autonomy and self-determination (the right to make choices) as key ethical principles.¹¹ The Black Mamas Matter Alliance (BMMA) has outlined 8 standards for the provision of holistic care for Black people, which can serve as a foundation for the development of ethical research initiatives¹²:

1. Recognize the historical experiences and expertise of Black women and families;
2. Listen to Black women;
3. Provide care through a reproductive justice framework;
4. Disentangle care practices from the racist beliefs in modern medicine;
5. Replace White supremacy and patriarchy with a new care model;
6. Empower all patients with health literacy and autonomy;
7. Empower and invest in paraprofessionals; and
8. Recognize that access does not equal quality care.

Evaluation of the BMMA ethical components of care within the context of traditional ethical principles may prove beneficial during various aspects of the research process. A discussion of ethical values, BMMA components, and the applicability to the research setting is outlined in this section. Other standards are considered and evaluated throughout the discussion.

Recognize the historical experiences and expertise of Black women and families: Veracity and accountability

There are countless records of researchers and clinicians who have performed unethical studies on Black individuals,^{3-5,13} thus entrenching the normalization of disrespect and racism into the medical and research

enterprise.^{14,15} Examples are plentiful such as the repetitive gynecological experiments of Dr Sims without anesthesia on slave women in Alabama (Anarcha, Lucy, and Betsy), or the unauthorized acquisition and subsequent commercialization of HeLa cells from Henrietta Lacks.^{4,13,14} The trauma of this history infiltrates the research enterprise and influences the emotional and mental experiences of Black people who desire to engage in research.⁵

Research teams must consider the influence of this history on the mental well-being of research participants and work to decolonize the systemic structures that perpetuate this harmful history. The research enterprise has traditionally been led by White medical, nursing, and public health scientists, with a lack of research teams led by or inclusive of researchers of color.¹⁶ It is critical to shift this research paradigm that has normalized Black subjectivity to expertise reserved to predominantly White research groups. Novel and innovative strategies for research developed, led by, and initiated by Black researchers and communities may prove beneficial in advancing the science and instituting effective strategies to ameliorate disparities in health outcomes.^{12,17} Utilizing a research model that centers Black voices ensures that ethically sound, relevant, and community-centered research studies are built on a tenet of beneficence, justice, and social responsibility.

Listen to Black women: Beneficence, respect, and patient autonomy

Black women have consistently reported feeling mistreated and unheard when receiving medical care during pregnancy.¹⁵ The experiences of Black women feeling unheard during participation in maternal health research have not been explicitly reported in the literature; however, it is reasonable to consider that similar experiences could occur during the research process. Research investigations focused on maternal morbidity and mortality are necessary, but Black participants may be more vulnerable when involved in these studies due to heightened concerns about the increased risk of dying in childbirth.¹⁸ Research teams must listen and respond with respectful and compassionate care while discussing alternatives in light of the concerns expressed by participants. When communicating about sensitive topics, it is important that the feelings of the participant are validated in a way that allows the person to feel honored, heard, and respected. This ensures that the research experience embodies the ethical principles of beneficence and respect. In addition, the research team can incorporate holistic care into the research process that centers Black voices, pro-

vides validation of the lived experience, and empowers the participant with information and choice to make decisions, thereby encouraging patient autonomy in research.^{12,17}

Replace White supremacy and patriarchy: Beneficence versus maleficence

An alternative perspective that some scholars could present to counter this discussion is that researchers who are actively engaged in developing studies focused on addressing maternal morbidity and mortality risk are not individuals who would perpetuate historical narratives or engage in racist and unethical behaviors. For example, supporters of Dr Marion Sims state that he was operating within the culture of that time and from a lens of beneficence.¹⁹ His study findings were reported to improve the lives of enslaved women, who potentially desired the treatment and may have been willing participants, given the suffering that often resulted from vesicovaginal fistula.¹⁹ In this example, the technique under research investigation was focused on the repair of fistulas in enslaved women that would improve their medical conditions, but the intent was to ensure that slave women could reproduce and ensure that the capitalistic system of slavery thrived.¹⁴ Colonial legislation of that time placed Black women childbearing as the central component to slavery as the laws mandated that the status of a child followed the matriarchal bloodline.¹⁴ As such, the intent of the research was not intended to improve the health of the women but to uphold a racist system that perpetuated maleficence (harm) and mistreatment. Researchers must carefully review research questions and methods to ensure that the intent of proposed initiatives truly benefits the community most affected and is not designed purely for personal or professional gain.

COMMUNITY DEVELOPED RESEARCH FRAMEWORKS AND METHODOLOGIES

Community engagement in the research process improves the quality of science and allows for multiple perspectives to be considered beyond those present in traditional research approaches.²⁰ Scientific inquiry typically involves researchers who develop research questions, write proposals, and disseminate information; however, community developed frameworks center the community as the expert in research design, implementation, and dissemination.²¹ The development of partnerships between academic researchers and community stakeholders is needed within the context of maternal mortality research. Utilizing a community-led approach is a practical way to address the BMMA recommendation to disentangle care practices and move

toward a process that respects collective expertise in solving health issues.

The utilization of community-driven research methods grounded in a reproductive justice framework will promote more equity in the design and implementation of research studies targeting health disparities including those focused on maternal morbidity and mortality. Examples of community-focused research frameworks and methods that have been shown to improve the research process among Black populations include the Research Protocol by Affected Communities (RPAC) Protocol and the Community Research Advisory Board.²²⁻²⁴ As noted in Table 1, the primary goal of these methods is to ground the research process from the inception of the research question through publication of the research findings within the community of individuals most influenced by the health outcome under investigation in the research study. The expertise and critical analysis of the health outcome of interest are driven by the community, not the research team. Use of such frameworks from the initial proposal development stage through the completion of the study has been found to improve relevance of results, increase enrollment and retention, and promote changes in clinical practice.²² The RPAC Protocol and the Community Research Advisory Board embody the BMMA ethical principle of empowering patients with health literacy and autonomy.

A clinically focused framework, designed by scholars of color and communities of Black women, that could be adapted to the clinical research process is the Cycle to Respectful Care tool. The model outlines a systematic method of dismantling biased practices and beliefs that promote racism.²⁵ The core of the model is centered on key values including Blackness, equity, reproductive justice, holistic maternity care, humanity, and love. As individuals move through various phases of the cycle, the likelihood of providing respectful maternity care is more likely. This approach could prove beneficial within the research context to assist research teams in identifying biases and making sure that research protocols embody respect, minimize harm, and center the research process on maintaining the dignity and respect of research participants.

DISCUSSION

Researchers interested in conducting research related to maternal morbidity and mortality must carefully examine the intent of doing the project, not just haphazardly develop studies because of funding opportunities. Utilization of a framework of reproductive justice coupled with community-driven research methodologies will ensure that Black people are centered in the research process. As such, models of care and initiatives designed

from the research will have a greater probability of producing equity in health outcomes while building trust within communities.

The role of the nursing workforce

A variety of themes and research gaps underlying the increasing rates of maternal mortality have been identified by national experts and include issues with data reporting and monitoring, obstetrical and health system factors, social determinants of health, and challenges with community engagement.^{26,27} As the largest health-care workforce, nurses interface daily with many of these factors and are vital to improving the health outcomes for Black pregnant populations.²⁸ Nurses are also involved in the research process and vital to the success of research studies. Clinical research nurses oversee the management of daily activities critical to the success of a research study including preparation of research protocols, recruitment, informed consent, protection of human subjects, and oversight of clinical research visits. Nursing scientists are working as independent investigators, focused on developing research questions and designing and implementing studies to address health disparities. Within the clinical context, the nurse is expected to manage the intersection of complex issues related to health, including complex topics related to racism, bias, and health equity. Given this expertise and breadth of focus, nurses are uniquely qualified to lead innovative care models to address the gaps contributing to the maternal mortality crisis. This can be further achieved by intentional development and training of clinical research nurses and scientists of color who can guide the development and implementation of effective research questions, frameworks, and methods.¹⁷

It is important that trust is developed between researchers and the communities that are affected by the health outcome of interest. Currently, 80% of the nursing workforce is non-Hispanic White, although racial and ethnic diversity has improved over the last 10 years.²⁹ Race alone does not determine the quality of care given; however, racial differences may decrease trust due to the historical grievances of past research experiences. Intentional efforts to restructure the research team to address disparities in participant-researcher racial concordance, with a focus on relationship building to encourage trust, may improve the experience of Black people during the research process.¹⁷ The desire for racial concordance is a valid experience commonly reported by Black women who experience poor birth outcomes.¹⁷ Representative researchers from the community of interest may be better equipped to navigate the complexities that may arise in Black maternal health studies.

Table 1. Community-focused research methods^a

Method	Purpose and format
RPAC Protocol ^b	<p>Purpose</p> <ul style="list-style-type: none"> • The RPAC protocol is a research protocol and strategic process of initiating research questions and priorities within communities of color.²² • The protocol is specifically focused on addressing research priorities in communities at high risk for preterm birth with the goal of developing partnerships between researchers, public health agencies, community leaders, and pregnant people/families most at risk for preterm birth. <p>Format of sessions and key topics covered</p> <p>Preparation</p> <ul style="list-style-type: none"> -Identify the research team including collaborators and members of the community of interest -Review the protocol and obtain IRB approval -Develop team roles -Invite 10-12 participants from the community of interest <p>Session 1: Developing research questions</p> <ul style="list-style-type: none"> -Center the session by meditation and deep breathing -Thank participants for coming to session and participating -Set basic ground rules for the process -Evaluate participants views, questions, and concerns about the health issue -Complete a thematic analysis of the proposed topics <p>Session 2: Prioritizing research questions</p> <ul style="list-style-type: none"> -Review topics brought up from session 1 -Use individual and group time to prioritize top research priorities -Debrief with participants about participating in the process <p>Session 3: Synthesizing results</p> <ul style="list-style-type: none"> -Review transcripts and recordings from previous sessions to prepare a document of findings -Generate a list of top research priorities
Community Research Advisory Board (CAB) ^b	<p>Purpose</p> <p>CABs utilize the knowledge of community members to provide insight into the research process from design, instrument development, recruitment strategies, research protocols, and dissemination. The toolbox described presents a process for the development of CAB guidelines through the Center for Indigenous Environmental Health Science Research with a focus of developing an accessible tool for diverse communities.²⁴</p> <p>4 Target areas outlined:</p> <ol style="list-style-type: none"> 1. Formation: Tools related to developing community representation and CAB membership, memorandas of agreement, and recruitment strategies 2. Operation: Approaches to develop leadership roles and responsibilities 3. Sustainability: Guidelines for CAB function and success 4. Evaluation: Methods to review CAB member satisfaction and experiences
Cycle to Respectful Care ^b	<p>Purpose:</p> <p>The Framework, developed through an iterative process involving Black birthing people, describes the process for training in anti-racist maternity care whether internalized or institutionalized. Although clinically focused, this model can be applied as a template for addressing issues in the provision of respectful research when working with Black populations.²⁵</p> <p>Core Values: Blackness, Birth equity, Professional oath, Holistic maternity care, Humanity, Love</p> <p>Process: The core values outlined connect to each step and mature as an individual moves through the process.</p> <p>Step 1. Waking up: Awareness of disparities via data or quality improvement information</p> <p>Step 2. Getting ready: Addressing personal beliefs and privilege</p> <p>Step 3. Reaching out: Awareness of provider bias and development of empathy; respect of pregnant patient's bodies, respecting emotional experiences, and addressing social determinants of health</p> <p>Step 4. Implementing with the provider community: Accountability and equity related to building trust and transparency via anti-racist practices, shared decision-making, and education</p> <p>Step 5. Coalescing with the local community: Working with the community and empowering patients with support and resources</p> <p>Step 6. Creating change: Transforming institutions and developing new cultures focused on prioritizing health equity, shared power, and reconciling harm resulting from systemic structures</p> <p>Step 7. Maintaining: Advocating for peers, investing in diverse leadership, and promoting transformation</p>

Abbreviations: CAB, Community Advisory Board; IRB, institutional review board; RPAC, Research Prioritization by Affected Communities Protocol.

^aFrom Yuan et al.²⁴ Copyright 2020 by the Johns Hopkins University Press. Adapted with permission of Johns Hopkins University Press.

^bFull details outlining the sessions and specific details are included in the referenced publications. The points mentioned here are a summary of the components presented in the articles.

CONCLUSION

Addressing the maternal morbidity and mortality crisis in the United States is critical, and the development of effective and ethical research strategies grounded in reproductive justice is needed to ensure that initiatives are appropriate and nontraumatizing for Black populations. Research teams must carefully evaluate the context and culture surrounding the research project and critically review research protocols to ensure that harm does not occur. Maintaining a research model that does not center the Black perspective or include that voice within the infrastructure of research team design and implementation upholds the narrative of White expertise and Black subjectivity. Researchers must carefully consider the complexity of engaging in research related to maternal mortality before developing projects, given the delicate nature and cultural components intersecting with the crisis. Funding availability and overall national interest in research related to maternal morbidity and mortality have increased; however, given the historical trauma and sensitive nature of the topic, researchers must evaluate research designs and methodologies more critically.

References

- Collier AY, Molina RL. Maternal mortality in the United States: updates on trends, causes, and solutions. *Neo-Reviews*. 2019;20(10):e561–e574. doi:10.1542/neo.20-10-e561.
- Hoyert DL. *Maternal Mortality Rates in the United States, 2019*. Hyattsville, MD: National Center for Health Statistics; 2021. <https://www.cdc.gov/nchs/data/hestat/maternal-mortality-2021/maternal-mortality-2021.htm>. Accessed January 16, 2021.
- Gamble VN. Under the shadow of Tuskegee: African Americans and health care. *Am J Public Health*. 1997;87(11):1773–1778. doi:10.2105/ajph.87.11.1773.
- Johns Hopkins Medicine. The legacy of Henrietta Lacks. <https://www.hopkinsmedicine.org/henriettalacks>. Published May 3, 2021. Accessed May 3, 2021.
- Scharff DP, Mathews KJ, Jackson P, Hoffsuemmer J, Martin E, Edwards D. More than Tuskegee: understanding mistrust about research participation. *J Health Care Poor Underserved*. 2010;21(3):879–897. doi:10.1353/hpu.0.0323.
- Britt AJ, Carlson NS, Joseph NT, Amore AD. The convergence of COVID-19 and systemic racism: an evaluation of current evidence, health system changes, and solutions grounded in reproductive justice. *J Midwifery Womens Health*. 2021;66(3):298–303. doi:10.1111/jmwh.13250.
- Gur RE, White LK, Waller R, et al. The disproportionate burden of the COVID-19 pandemic among pregnant Black women. *Psychiatry Res*. 2020;293:113475. doi:10.1016/j.psychres.2020.113475.
- Doody O, Noonan M. Nursing research ethics, guidance and application in practice. *Br J Nurs*. 2016;25(14):803–807. doi:10.12968/bjon.2016.25.14.803.
- Epstein B, Turner M. The nursing code of ethics: its value, its history. *Online J Issues Nurs*. 2015;20(2):4.
- US Department of Health and Human Services. 45 CFR 46. <https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/index.html>. Accessed January 19, 2022.
- Scott KA, Britton L, McLemore MR. The ethics of perinatal care for Black women: dismantling the structural racism in “mother blame” narratives. *J Perinat Neonatal Nurs*. 2019;33(2):108–115. doi:10.1097/jpn.0000000000000394.
- Black Mamma Matter Alliance. Setting the standard for holistic care of and for Black women. http://blackmamamatter.org/wp-content/uploads/2018/04/BMMA_BlackPaper_April-2018.pdf. Accessed April 30, 2021.
- Wailoo K. Historical aspects of race and medicine: the case of J. Marion Sims. *JAMA*. 2018;320(15):1529–1530. doi:10.1001/jama.2018.11944.
- Owens DC, Fett SM. Black maternal and infant health: historical legacies of slavery. *Am J Public Health*. 2019;109(10):1342–1345. doi:10.2105/ajph.2019.305243.
- Vedam S, Stoll K, Taiwo TK, et al. The Giving Voice to Mothers study: inequity and mistreatment during pregnancy and childbirth in the United States. *Reprod Health*. 2019;16(1):77. doi:10.1186/s12978-019-0729-2.
- Wren Serbin J, Donnelly E. The impact of racism and midwifery's lack of racial diversity: a literature review. *J Midwifery Womens Health*. 2016;61(6):694–706. doi:10.1111/jmwh.12572.
- Altman MR, McLemore MR, Oseguera T, Lyndon A, Franck LS. Listening to women: recommendations from women of color to improve experiences in pregnancy and birth care. *J Midwifery Womens Health*. 2020;65(4):466–473. doi:10.1111/jmwh.13102.
- Centers for Disease Control and Prevention. Working together to reduce Black maternal mortality. <https://www.cdc.gov/healthequity/features/maternal-mortality/index.html>. Accessed January 19, 2022.
- Wall LL. The medical ethics of Dr J Marion Sims: a fresh look at the historical record. *J Med Ethics*. 2006;32(6):346–350. doi:10.1136/jme.2005.012559.
- Springer MV, Skolarus LE. Community-based participatory research. *Stroke*. 2019;50(3):e48–e50. doi:10.1161/strokeaha.118.024241.
- Sanders Thompson VL, Ackermann N, Bauer KL, Bowen DJ, Goodman MS. Strategies of community engagement in research: definitions and classifications. *Transl Behav Med*. 2021;11(2):441–451. doi:10.1093/tbm/ibaa042.
- Franck LS, McLemore MR, Cooper N, et al. A novel method for involving women of color at high risk for preterm birth in research priority setting. *J Vis Exp*. 2018;(131):56220. doi:10.3791/56220.
- Wallerstein N, Duran B. Community-based participatory research contributions to intervention research: the intersection of science and practice to improve health equity. *Am J Public Health*. 2010;100(suppl 1):S40–S46. doi:10.2105/ajph.2009.184036.
- Yuan NP, Mayer BM, Joshweseoma L, Clichee D, Teufel-Shone NI. Development of guidelines to improve the effectiveness of community advisory boards in health research. *Prog Community Health Partnersh*. 2020;14(2):259–269. doi:10.1353/cpr.2020.0026.
- Green CL, Perez SL, Walker A, et al. The Cycle to Respectful Care: a qualitative approach to the creation of an actionable framework to address maternal outcome disparities. *Int J Environ Res Public Health*. 2021;18(9):4933. doi:10.3390/ijerph18094933.
- Chinn JJ, Eisenberg E, Artis Dickerson S, et al. Maternal mortality in the United States: research gaps, opportunities, and priorities. *Am J Obstet Gynecol*. 2020;223(4):486–492.e6. doi:10.1016/j.ajog.2020.07.021.

27. Crear-Perry J, Correa-de-Araujo R, Lewis Johnson T, McLemore MR, Neilson E, Wallace M. Social and structural determinants of health inequities in maternal health. *J Womens Health (Larchmt)*. 2021;30(2):230–235. doi:10.1089/jwh.2020.8882.
28. McMillian-Bohler J, Richard-Eaglin A. Uprooting racism: the role of nurses in cultivating improved maternal outcomes for Black and African American women. *Creat Nurs*. 2021;27(1): 61–65. doi:10.1891/cnr-d-20-00066.
29. Zangaro GA, Streeter R, Li T. Trends in racial and ethnic demographics of the nursing workforce: 2000 to 2015. *Nurs Outlook*. 2018;66(4):365–371. doi:10.1016/j.outlook.2018.05.001.