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HIV molecular epidemiology: tool of oppression or empowerment?

Stuart Rennie, PhD [Professor],

UNC-Chapel Hill, Social Medicine, 333D MacNider Hall, 333 South Columbia St., Chapel Hill, 27599 United States

Dr Kristen Sullivan,

University of North Carolina at Chapel Hill, Chapel Hill, 27515 United States

Dr Ann Dennis

University of North Carolina at Chapel Hill, Chapel Hill, 27515 United States

Molldrem and Smith are to be commended for their insightful analysis of a public health practice that has received little attention among bioethicists: the use of molecular HIV surveillance (MHS) and cluster detection and response (CDR) for epidemiology and prevention. We agree with the authors that these methodologies raise potential issues of justice in relation to marginalized and vulnerable groups, and the essential need for meaningful, responsive community engagement around these practices and public health surveillance generally. However, we argue that their analysis underplays a number of key considerations that are important for a nuanced ethical assessment of MHS and CDR. These considerations fall under the broad categories of consent, risk/benefit, and justice.

Consent.

As Molldrem and Smith point out, MHS utilizes blood samples from drug resistance testing collected during routine HIV care. This re-use for public health purposes is typically conducted without the patient's consent, or as the authors put it, without a 'mechanism of refusal.' But they do not mention a central reason why consent is not asked: participation bias. If MHS analyses can only include samples from those who consented to having their blood used for this purpose, the resultant 'map' of genetic sequences would be full of gaps. If the level of refusal is high enough, the MHS analysis could be rendered useless. And no matter how you set up the consent process, be it dynamic consent or opt-out, participation bias remains a vexing problem. So when Molldrem and Smith write that, "Any effort that supports an increase of individuals' rights over their data would be welcome", we wonder about the 'any': are efforts that compromise the validity and utility of MHS for surveillance and prevention also welcome? We are not arguing here that individual consent for public health uses of samples for MHS should not be explored; we are bringing up a known and ethically significant cost associated with a mechanism of refusal in this context that deserves due consideration. There are further sticky questions about whether and how consent should

be obtained when researchers make use of surveillance data previously collected by public health agencies, but here too the issue of participation bias needs to be part of the conversation.

Risk/benefit.

Molldrem and Smith argue that the use of MHS in HIV research and surveillance is ethically questionable, because the risk/benefit relationship is unfavorable. MHS carries a number of potential risks (such as loss of privacy, criminalization, stigma, and discrimination) to which marginalized individuals and groups are disproportionately exposed, and there is insufficient evidence for its benefits. Their discussion of directionality is intended to bring this imbalance into sharp relief, since being able to infer directionality of HIV transmission can increase risks to individuals and communities, while the benefits of ascertaining directionality are unclear. We would like to make two points:

(1) Evaluating the risk/benefit relationship of emerging public health interventions on the basis of evidence is complicated.

The authors identify a number of potential risks and concerns, but (as the authors occasionally admit) there is currently little evidence about their probability, magnitude or prevalence.

On the benefit side, the authors argue that MHS and CDR have been scaled up on a national policy level without respect to the standard benchmarks of evidence, and therefore we do not have a clear idea of what public health benefits they can provide. We agree that the scale up was hasty, and the implementation of MHS and CDR should be the object of continuous, critical study. But the debate is far from closed about what kinds of evidence are sufficient before widespread dissemination of a public health practice. Certainly, molecular epidemiology has shown great utility in characterizing the dynamics of regional, national, and cross-national HIV transmission, as well as emerging epidemics and transmission of drug-resistance (Oster et al. 2015; Wang et al. 2015; Wertheim et al. 2016; Kühnert et al. 2018). Additionally, there are a number of pilot projects and outbreak interventions using MHS and CDR which show promise in regard to HIV surveillance and outbreak response (Golden et al. 2019; Samoff et al. 2020; Alpren et al. 2020). In short, the picture of risks and benefits is currently too clouded to state categorically that their relationship is unbalanced.

(2) The discussion of transmission directionality must clarify the phylogenetic “tools” terminology to more accurately understand the complexity of HIV genomic data, bioinformatic software, and utility in public health contexts.

Without a clear understanding of the technical capacities and limitations of current, widespread MHS data, software and interpretation, ethical analysis (including mitigation strategies) will be based on misleading simplifications.

The authors assert that the claim “‘molecular surveillance data alone’ cannot be used to determine directionality” is spurious. We challenge this assertion, and reiterate that MHS “tools” are not suited to make transmission determinations involving individuals within specific genetic clusters. This is important, for one, to clarify that the use of MHS tools does

not inevitably imply that determinations of transmission directionality are possible, nor is their utility for public health purposes based on such potential. Methods to mitigate such possibilities, including data smoothing, need further development to determine best practices in application (Mehta, Schairer, and Little 2019).

Bioinformatic or phylogenetic “tools” are software and statistical models developed to compare, analyze, and interpret genomic data. The quality and type of genomic data will affect the output and interpretation. CDC’s MHS uses consensus sequences, where the entire viral population in an individual is reduced to one sequence in partial region of the HIV genome which is insufficient to support directionality. The popular HIV-TRACE package does not in fact include methodology to estimate directionality; the analyses in HIV-TRACE are based on pairwise comparisons of sequence similarity with no reconstruction of their evolutionary relationships. Additional data are needed to estimate transmission direction, which on a population-level is important for estimating transmission risk. However, these methods are not robust or appropriate to apply to individuals within CDRs. While Molldrem and Smith describe how the visual characteristics of the network diagrams produced may be incorrectly interpreted to infer directionality of transmission, there is no indication of widespread misinterpretation in research or practice. If anything, this serves to highlight the known need for robust training in the interpretation of these complex visuals.

Certainly, the risks of such determinations of transmission directionality are amplified in contexts where criminalization of HIV transmission exists. Policy-level mitigation strategies, including updating state statutes and regulations to prohibit health departments from disclosing individually identifiable health information to law enforcement, should receive fulsome consideration (Crowley and Bland 2019). Additionally, with recent updates to the 21st Centuries Cure Act, sensitive research data collected or used with federal funding involving even a “very small risk” of being potentially identifiable are protected by automatically issued Certificates of Confidentiality which prohibit researchers to release data to external entities, including law enforcement (Dawson et al. 2020). The strength of this “legal firewall” between public health research and law enforcement remains to be seen (Wolf and Beskow 2019).

Justice.

Molldrem and Smith are concerned that the use of MHS for surveillance poses added risks to marginalized and vulnerable groups, as well as constituting a regime of control, particularly when MHS guides CDR ‘direct prevention’ activities in communities. We share these concerns, while adding that there is another side to the coin. The authors discuss CDR without providing concrete examples, giving a general impression of these interventions as oppressive and unwanted. In practice, CDR responses are multifaceted and often include provision of increased/redirected resources for routine, evidence-based field service activities including bridge counseling, i.e. assisting individuals lost-from-care link back to care by identifying barriers and support services such as transportation and substance abuse treatment. One can see this clearly in Data-to-Care initiatives that try to identify persons living with HIV who have interrupted their treatment, and offer them support to rejoin care. Are such practices oppressive or empowering? There is no one clear answer. Some people

may appreciate this form of assistance, particularly when they have fallen out of care due to forces beyond their control, or when they did not consider themselves at risk for HIV acquisition. Others will regard such interventions as unjustified state intrusions into their lives. To complicate matters further, there is the ethical question of what public health agencies should do when, on the basis of MHS, they identify an outbreak. Do they have a duty to conduct CDR? Or would it be better, ethically speaking, to revert back to the less proactive style of epidemiology, itself often criticized for measuring rather than intervening?

The authors rightly warn against optimism about new surveillance technologies blunting ethical assessments of their potential for harm and injustice. Bioethicists should not act as their cheerleaders. On the other hand, pessimism and suspicion about public health practices, as we have seen with the Covid-19 pandemic, is another extreme best avoided.

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