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Just Research in an Unjust World: Can Harm Reduction Be an Acceptable Tool for Public Health Prevention Research?

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In recent years, two research endeavors, one international, one domestic, have been the focus of considerable ethics debate. The first was a series of HIV perinatal transmission studies conducted in the mid-1990s in resource-poor countries.[1] The second was a lead abatement trial initiated in the early 1990s in low-income housing units in Baltimore.[2] Both studies were accused of

[1] E. M. Connor et al., "Reduction of Maternal–Infant Transmission of Human Immunodeficiency Virus Type 1 with Zidovudine Treatment: Pediatric Aids Clinical Trials Group Protocol 076 Study Group," *NEJM* 331/18 (1994), 1173–80; R. S. Sperling et al., "Maternal Viral Load, Zidovudine Treatment, and The Risk of Transmission of Human Immunodeficiency Virus Type 1 from Mother to Infant. Pediatric Aids Clinical Trials Group Protocol 076 Study Group," *NEJM* 335/22 (1996), 1621–9.

[2] M. R. Farfel and J. J. Chisolm, Jr., "Health and Environmental Outcomes of Traditional and Modified Practices for Abatement of Residential Lead-Based Paint," *American Journal of Public Health*, 80/10 (1990), 1240–5; M. R. Farfel, J. J. Chisolm, Jr., and C. A. Rohde, "The Longer-Term Effectiveness of Residential Lead Paint Abatement," *Environmental Research*, 66/2 (1994), 217–21; M. R. Farfel and J. J. Chisolm, Jr., "An Evaluation of Experimental Practices for Abatement of Residential Lead-Based Paint: Report on a Pilot Project," *Environmental Research*, 55/2 (1991), 199–212.

violating research ethics guidelines because, it was alleged, participants, or some participants, did not receive the best interventions available for the condition in question. Indeed, both studies have been compared to the U.S. Tuskegee study,[3] contemporary shorthand for the most severe unethical conduct in human research. Public health professionals, however, have defended both studies, saying they not only were ethically acceptable, but were ethically required.[4]

Both case studies in question were examples of public health prevention research. Specifically, researchers were trying to identify cheaper, simpler, and more accessible prevention strategies as alternatives to existing approaches, as existing approaches were not reaching target populations. In the 1990s, AZT was shown to dramatically reduce maternal infant transmission but was projected to have little impact on the 1,000 daily global births of HIV-infected children since its cost and complexity precluded its accessibility in the developing world.[5] As long ago as 1931 the use of lead paint was banned in Europe due to its deadly effects on children;[6] nonetheless, in the 1990s, proper lead abatement remained as inaccessible to most at risk families in Baltimore City as AZT was to poor, global women. The ethics question raised by these studies is whether background conditions of access should prompt public health professionals to seek alternate strategies that might be more accessible, albeit potentially less effective; or whether such a response makes scientists themselves morally culpable, seeming to accept and condone the injustices that exist. To that end, this chapter will take on

[3] M. Angell, "The Ethics of Clinical Research in The Third World," *NEJM* 337/12 (1997), 847–9; *Ericka Grimes* v *Kennedy Krieger Institute Inc.* 128 (2000), available at <http://www.courts.state.md.us/opinions/coa/2001/128a00.pdf>; R. J. Levine, "The 'Best Proven Therapeutic Method' Standard in Clinical Trials in Technologically Developing Countries," *Journal of Clinical Ethics*, 9/2 (1998), 167–72.

[4] F. Luna, "Is 'Best Proven' a Useless Criterion?," *Bioethics*, 15/4 (2001), 273–88; H. Varmus and D. Satcher, "Ethical Complexities of Conducting Research in Developing Countries," *NEJM* 337/14 (1997), 1003–5; World Health Organization (WHO), *Recommendations from the Meeting on Mother-to-Infant Transmission of HIV by Use of Antiretrovirals* (Geneva: World Health Organization, 1994); L. F. Ross, "In Defense of the Hopkins Lead Abatement Studies," *J Law Med Ethics*, 30 (2002), 50–7.

[5] WHO, *Recommendations Use of Antiretrovirals.*

[6] J. Pollak, "The Lead-Based Paint Abatement Repair and Maintenance Study in Baltimore: Historic Framework and Study Design," *Journal of Health Care Law and Policy*, 6/1 (2002), 89–108; A. Spake and J. Couzin, "In the Air That They Breathe. Lead Poisoning Remains a Major Health Hazard for America's Children," *US News and World Report*, 127/24 (1999), 54–6.

the question of whether and/or how public health researchers can conduct just research in background contexts of extraordinary injustice.

It should be said at the outset that the purpose of discussing these cases here is not to revisit the long debates that surrounded those particular studies. Rather, these studies are paradigmatic cases of community-based public health prevention research and the issues they raise emerge in hundreds of other studies every year. The publicity given to these two studies, however, can be a springboard to broader discussions of acceptable approaches for public health prevention trials broadly. The conclusions and recommendations provided here are intended to apply to this larger body of research, not to the two studies that catalyzed the discussion.

This chapter is divided into five sections. The first section provides brief background on the two studies in question and summarizes arguments put forward in ethics debates about them. The second section calls for additional ethics guidance for public health prevention studies, suggesting that existing research ethics guidelines have failed to address such research of this type. The third section will introduce the concept of harm reduction as a possible methodologic tool for public health researchers and discuss why engaging in a harm reduction approach might be useful. The fourth section will provide a set of criteria for determining when harm reduction research is and is not morally acceptable. And, finally, the fifth section tries to anticipate and address criticisms to this same approach. Ultimately, it will be argued that harm reduction research should be an ethically acceptable tool in the public health prevention research "toolbox" but also that it will be justifiable only in narrowly defined circumstances. One can easily imagine how readily harm reduction as a research approach could be exploited. To that end, the chapter provides criteria that attempt to distinguish investigations that merely are expedient from investigations with reasonable likelihood of advancing domestic and global public health.

I. Case Studies

1. International Perinatal HIV Transmission Trials

In 1994, the US-sponsored AIDS Clinical Trials Group study 076 and a separate French study demonstrated that administering the antiretroviral

drug zidovudine (AZT) to pregnant HIV-infected women and to their newborn babies greatly reduced the likelihood that the babies would be HIV-infected.[7] This "076 regimen", consisting of AZT tablets for HIV-infected women during the second and third trimesters of their pregnancies, intravenous AZT during labor and delivery, and oral AZT drops for newborns for the first six weeks of life, immediately became the standard of care for HIV-infected pregnant women in the US and in Europe.[8] In a context where children were dying daily from HIV infection, the 076 results were so dramatic—a reduction in HIV Maternal Infant transmission (MIT) from 25 percent to 8 percent—that study findings were translated into clinical practice with an urgency rarely experienced after a single clinical trial.

Unfortunately, this public health advance held little immediate relevance for the poorer regions of the world, where the vast majority of perinatal HIV existed. First, the 076 regimen was estimated to cost about $800 per mother–infant pair,[9] while resource-poor countries often spend $5–30 dollars per year on health care per capita. Second, even if the drug could be donated, the infrastructure requirements of the full regimen (receiving prenatal care as early as the second trimester, early HIV testing, and intravenous equipment available for all HIV-infected women's births) were unrealistic in most resource-poor environments. Third, HIV-infected women in Africa and Asia were more likely to be breastfeeding their children—a practice with its own important public health benefit—yet it was not clear the degree to which breastfeeding might negate the benefits of the 076 intervention. As a result, the World Health Organization (WHO) convened a consensus conference to determine the implications of the 076 results for resource-poor countries. The consensus document acknowledged that, due to the expense and complexity of the 076 regimen, "no global recommendations regarding the use of ZDV [zidovudine, also known as AZT] to prevent maternal to infant transmission of HIV can be made." Instead, a series of research recommendations emerged, most notably that "it is

[7] Connor et al., "Reduction of Maternal–Infant Transmission"; Sperling et al., "Maternal Viral Load", *NEJM* 335/22 (1996), 1621–9.

[8] Centers for Disease Control and Prevention, "Recommendations of the U.S. Public Health Task Force on the Use of Zidovudine to Reduce Perinatal Transmission of Human Immunodeficiency Virus," *Morbidity and Mortality Weekly Report*, 43(RR-11) (1994), 1–21; WHO, *Recommendations Use of Antiretrovirals*.

[9] Varmus and Satcher, "Ethical Complexities."

essential to explore simpler and less costly drug regimens [in resource-poor countries] . . . Such regimens . . . should be urgently studied in randomized controlled trials . . . placebo controlled trials offer the best option."[10] The document also said that studies "should be part of a research strategy which may reasonably be expected to lead to interventions which will be affordable, feasible, and sustainable in the same setting." A series of eighteen trials was planned in developing countries ranging from vitamin A supplementation to short-course AZT trials.[11]

Three years later (April 1997), Public Citizen Health Research group, a Washington-based advocacy organization, accused HIV researchers and funders of conducting unethical research because most of the new global trials included a placebo arm. Placebo controls, they argued, exploited poor women participating in these global trials, and created a double standard, as placebos no longer would have been allowable in U.S. prevention trials of HIV MIT prevention. Public Citizen instead advocated equivalency trials for poor countries, where simpler, cheaper regimens would be tested against the full 076 regimen.[12] Researchers and funders responded to Public Citizen by citing methodologic justifications for placebos, suggesting that equivalency trials would be inconclusive and also would take considerably longer to conduct, thus delaying the delivery of potentially effective HIV interventions to global communities.[13]

2. Baltimore Lead Study

The 'Lead-Based Paint Abatement and Repair and Maintenance Study' (R & M Study) was initiated in 1993 as the third in a series of lead poisoning prevention studies conducted in at risk Baltimore neighborhoods. As background, it had been known for at least half a century that lead was dangerous to children.[14]

[10] WHO, *Recommendations Use of Antiretrovirals*.

[11] P. Lurie and S. M. Wolfe, "Unethical Trials of Interventions to Reduce Perinatal Transmission of the Human Immunodeficiency Virus in Developing Countries," *NEJM* 337/12 (1997), 853–6.

[12] Parenthetically, designing such a trial, whereby half the women would receive an intervention explicitly expected to be less effective than 076, was not addressed as an ethical dilemma by Public Citizen.

[13] Varmus and Satcher, "Ethical Complexities"; B. R. Bloom, "The Highest Attainable Standard: Ethical Issues in Aids Vaccines," *Science*, 279/5348 (1998), 186–8.

[14] Pollak, "Lead-Based Paint Abatement Study."

Thomas and Blackfan reported the first case of child lead poisoning in Baltimore in 1914,[15] and in 1921, the International Labor Organization in Geneva sponsored the White Lead Paint Convention to limit the amount of lead in paint as well as the places where lead paint could be used.[16] While the new use of lead paint in residences was banned in Europe in 1931,[17] a similar prohibition was not enacted in the United States until 1978.

In the 1990s 95 percent of Baltimore houses were built before the 1978 ban on the use of lead paint.[18] Thus, most children in Baltimore lived in houses with considerable lead paint. In poor neighborhoods, where housing often was in poor condition, children were at highest risk of lead poisoning from flaking paint and lead dust.[19] At the time, the Centers for Disease Control and Prevention (CDC) considered a blood lead level of 10 μg/dL to pose a risk to children. In Baltimore City in the early 1990s, blood elevations over this threshold level were at 10–15 times the national rate. In high-risk Baltimore neighborhoods, elevations were at 20–30 times the national rate, with 60 percent of children having levels over the 10 micrograms threshold. Further, fewer than half of Baltimore City children were being screened for lead levels by health care providers.[20] And while it had been known for decades that children were being poisoned in older and lower-income Baltimore neighborhoods, there was essentially no affordable new housing or completely abated housing. Despite considerable advocacy, no city, state, or federal governments in the United States mandated *preventive abatement* of any sort. Indeed, not only were landlords not required to engage in any abatement; they were not, until 1996, even required to inform residents of lead paint risks in the homes they were about to rent.

Dr. Julian Chisolm was a physician and researcher at the Kennedy-Krieger Institute in Baltimore, a non-profit institute specializing in developmental disease and disabilities. Dr. Chisolm, as a clinician, treated children suffering from the effects of lead poisoning. In the early 1980s, legislation did exist to require "therapeutic abatement." That is, abatement was required in the homes of children already found to have lead poisoning. Dr. Chisolm

[15] Henry M. Thomas and K. D. Blackfan, "Recurrent Meningitis Due to Lead in a Child of Five Years," *American Journal of Diseases of Children*, 8 (1914), 377–80.

[16] International Labor Organization, Convention concerning the use of white lead in painting. General Conference of the International Labor Organization, 1921. Enacted 1923.

[17] Pollak, "Lead-Based Paint Abatement Study."

[18] Ibid. [19] Ibid. [20] Ibid.

began to notice that, in following these children clinically, their blood lead levels often *rose* during the year abatement was implemented.[21] Thus, in 1984–5, Dr. Chisolm and his colleague Dr. Mark Farfel conducted their first collaborative study, demonstrating that commonly used methods of abatement (such as burning, sanding, and stripping of lead paint, with no worker training about occupant protection) caused an *increased* risk of lead poisoning, given that lead dust was created through the process.[22] This led to a change in abatement standards, first in Baltimore City in 1987, in Maryland in 1988, and federally in 1995, requiring new practices for lead paint abatement in homes. It now became forbidden to burn and scrape paint, and new standards required worker training, worker and occupant protection, and proper containment and disposal of debris.

A follow up study conducted in vacant homes revealed that alternative abatement strategies (including sealing and covering lead paint, dust containment, replacement of windows, sanding of floors to make them smooth and thus cleanable, and the use of high-efficiency particle air (HEPA) vacuums) were considerably safer and more effective at reducing household lead dust levels.[23] A second follow up study three years later showed that these effects were sustained rather than temporary, with household dust levels in these vacant homes reduced, on average, by approximately 90 percent.[24] Thus, these studies documented significant reduction, but not total elimination, of lead dust.[25] Abatements in these vacant homes generally cost $12–15,000 per home. As a result of this work, Baltimore City began a pilot project of lead reduction, in consultation with Drs. Chilsolm and Farfel. Due to the high cost of these new abatement methods, however, only a few dozen homes were improved through this City program, and indeed the cost of abatement often exceeded the value of some of these dwellings.[26] Unfortunately, legislative proposals calling for mandatory *preventive* abatement of rental properties in Baltimore City, based on these research findings, were repeatedly defeated.

In the early 1990s, recognizing that abatement was expensive while most lead poisoning occurred in low-income settings, several federal agencies

[21] Farfel, personal communication Oct 14, 2005.
[22] Farfel and Chisolm, "Health and Environmental Outcomes."
[23] Farfel and Chisolm, "An Evaluation of Experimental Practices."
[24] Ibid.
[25] Pollak, "Lead-Based Paint Abatement Study."
[26] Ibid.

called for research proposals assessing the effectiveness of different types of lead reduction strategies.[27] As part of this initiative, the Environmental Protection Agency (EPA) in 1993 funded the "Repair and Maintenance" (R & M) Study to be conducted in high-risk Baltimore neighborhoods. The goal of this study was to measure both short-term and long-term effects on household and blood lead levels of three different abatement strategies, all employing methods shown in the 1991 study to be effective, One approach cost approximately $1,650, another approximately $3,500, and the last approximately $6,000–7,000. Two additional groups of homes were included in the study as controls: houses built after 1978 (and thus free of lead paint) and houses from the City's prior abatement pilot project, whereby homes had received the comprehensive $12,000 abatement intervention. Families in all five arms of the study provided consent for monitoring of household lead dust levels and blood lead levels from the children at six-month intervals. It is highly likely that no abatement, and none of the accompanying education and ongoing monitoring, would have happened without the study.

This study found that, while the most intensive level of abatement was the most effective, all three experimental arms reduced house dust lead levels by more than 90 percent and children who entered the study with elevated blood lead levels, on average, experienced a statistically significant decrease in blood lead concentration over time. Based on this study's methods, HUD awarded thirty additional contracts around the country in fourteen cities to implement comparable interventions and to compare household and blood lead levels from various abatement strategies.

After the study was over, however, two families brought lawsuits. One (Higgins) charged that they were never informed of the risks of the study and the possibility of continued lead exposure in their home. The other family (Grimes) charged that results regarding blood lead levels were not shared with the parents in a timely manner. The judge issued a strongly worded ruling revealing his view that the study, as designed, was unethical. Indeed, his ruling went beyond the particular charges, suggesting that researchers were leading participants to their death, again invoking the analogy of Tuskegee and issuing inflammatory language like, "the researchers intended that the children be the canaries in the mines, but never clearly told the

[27] Pollak, "Lead-Based Paint Abatement Study."

parents."[28] This study prompted its own series of debates in the ethics world and precipitated the creation of a National Academy of Sciences panel to investigate the ethics of prevention research of this sort.[29]

II. The Need for Additional Ethics Guidance for Public Health Prevention Research

Assumptions behind existing research ethics guidelines may limit their ability to resolve dilemmas. In debates about the perinatal HIV trials, those who believed trials were ethical as designed and those who believed them to be completely unethical both invoked the Declaration of Helsinki as supporting their views. This led to international efforts to change language in the document in an attempt to eliminate ambiguities. And while such efforts, lengthy and contentious as they were,[30] resulted in a revision, it is not clear that the revisions provide clear moral or practical direction for researchers conducting studies of this sort. One might conclude that another revision is needed, or that guidelines are intended only to outline broad ethical norms. Our conclusion is different. We suggest that, when research ethics guidelines first were written thirty to forty years ago, they were responding to a very particular set of research problems that had captured the public's attention: lack of informed consent, lack of prior review, and potential exploitation of captive and/or vulnerable populations. The effect of the guidelines, and of the regulations that followed, over the last few decades, has been stunning in those particular domains. Research norms now assume that research will not be conducted without prior review and without informed consent, and researchers know they must justify the use of vulnerable populations in their research.

[28] *Ericka Grimes* v *Kennedy Krieger Institute Inc.*; *Myron Higgins, a minor, etc.,* et al. v. *Kennedy Krieger Institute, Inc.* 129. (2000), available at <http://www.courts.state.md.us/opinions/coa/2001/128a00.pdf>.

[29] B. Lo, B. and M. E. O'Connell, *Committee on Ethical Issues in Housing-Related Health Hazard Research Involving Children, Youth and Families. Ethical Considerations for Research on Housing-Related Health Hazards Involving Children* (Washington, DC: National Academies Press, 2005).

[30] C. Weijer and J. A. Anderson, "The Ethics Wars: Disputes over International Research," *Hastings Center Report*, 31/3 (2001), 18–20; S. M. Tollman, H. Bastian, R. Doll, L. J. Hirsch, and H. A. Guess, "What Are the Effects of the Fifth Revision of the Declaration of Helsinki?," *British Medical Journal*, 323/7326 (2001), 1417–23.

At the same time, research ethics guidelines, while responsive to the prevailing ethics challenges at the time, seem to be based on two assumptions about why ethics problems occur in human research. Both of these assumptions, I would argue, make the guidelines less relevant to the particular challenges posed by public health prevention studies such as the lead and HIV cases.

Research ethics guidelines and regulations crafted thirty to forty years ago first seemed to assume that research violations emerge as a result of researchers' individual or collective zeal for scientific discovery. Scientists, in their quest for answers, might unwittingly compromise subjects' rights and welfare and exploit available yet vulnerable populations. Guidelines, in turn, were crafted to articulate a shared societal norm for research ethics in order to guard against the moral pitfall to which they believed research was most vulnerable: individual researchers' inability to recognize when they were crossing a moral divide, blinded by their own intellectual enthusiasm.

Second, research ethics guidelines seem to assume an "idealized" paradigm for how research fits in to scientific progress: research is undertaken to solve important health problems; once each problem is solved, society benefits, and science can move on to other health challenges. Guidelines remind researchers that, in their pursuit of answers to new scientific questions, they may not deny already proven interventions to research subjects. Implicit in guidelines is the assumption that, absent the research, the subject would have been provided the best proven treatment; the only reason a research subject would not access the best known treatment during research, then, is through the actions, again, of an overly zealous researcher, who might deny it to them or ask them to go off of it for the sake of science. Not addressed in the research ethics guidance was the far more likely explanation, at least in global public health research today, for why a research subject might not access proven interventions. To wit, widespread economic, political, and social structures themselves either create or permit inequities in access to flourish. Local, national, and international injustices explain why, before researchers even enter the picture, poor families in Baltimore are still offered rental homes dripping with lead, and women and children in poor countries were assumed in 1994 to have no chance of accessing the extraordinary public health advance of AZT to prevent MIT of HIV. Research ethics guidance is needed, then, on how to evaluate studies

designed to reduce public health problems that exist because there is no political will to allocate the resources needed to implement already proven strategies.

If this assumption is accurate, investigators and ethics boards need guidance on how and when it is acceptable morally to test interventions that may be cheaper or simpler than existing, proven ones, proposed *only because of* the extraordinary economic and social disparities that flourish in our society. With a snap of the fingers, millions of children in Africa and Asia could avoid HIV-infection, and millions of children in the United States could avoid the brain damage associated with lead poisoning. When this does not happen, however, how can we determine what is morally acceptable practice for scientists whose research questions emerge, in great part, only as a result of neglect in the policy world. The research questions examined in the lead and HIV trials, presumably, only existed thanks to the global denial of effective interventions to those who need them. Researchers are on shaky moral terrain, however, when they venture into contexts of extraordinary economic and political inequity. For this reason, clear frameworks and guidance are needed to ensure that researchers are reducing, rather than exacerbating, the considerable moral harm that occurs when public health improvement is denied simply because of a lack of global will. Without such guidance, it will be difficult to differentiate research that is likely to be exploitive or expedient from research that is likely to improve the public's health.

III. Harm Reduction as a Strategy for Public Health Research

Harm reduction is a strategy that is increasingly accepted and implemented in public health practice. Harm reduction in public health can be defined as any policy, program, service, or action that works to reduce, rather than eliminate, harms to health for individuals or communities.[31]

[31] R. Newcombe, "The Reduction of Drug Related Harm: A Conceptual Framework for Theory, Practice and Research," in *The Reduction of Drug Related Harm*, ed. P. O'Hare et al. (London: Routledge, 1992).

Harm reduction is based on the assumption that, where the underlying causes of public health burden (i.e. widespread morbidity/mortality) remain difficult to eliminate, intervening to reduce some of the adverse health consequences of such root problems can result in a "net reduction in harm" to affected communities.[32] Harm reduction is intended to be *pragmatic*, in terms of providing a more feasible option, and to *prioritize goals*, focusing on the immediate need to protect individuals from harm, while recognizing that it fits into a larger hierarchy of important public health goals.[33]

Harm reduction has received the greatest publicity in practice contexts such as needle exchange to prevent HIV infection among drug users and provision of contraceptives and condoms to adolescents to prevent teen pregnancy and HIV. Harm reduction, like much of public health, is inherently consequentialist: it assumes that even incremental improvement in public health outcomes is to be valued; it also is practical, suggesting that one has a responsibility to change what can be changed, while continuing to find strategies to address the larger problems.

While harm reduction in public health practice is a generally accepted tool among public health professionals, it has been controversial more broadly, particularly when, like with the examples above, it involves practices like sex and drugs that carry significant moral and political overtones. As such, public health practitioners have been accused of being indifferent to or, even worse, complicit with disquieting and harmful behaviors.

As a methodologic strategy for *research,* however, harm reduction seems to be absent from the literature. Based on definitions of harm reduction in practice, harm reduction research might be defined as an investigative strategy to measure the effectiveness of potentially promising harm reduction strategies under controlled conditions. The goal is to determine whether strategies are effective at reducing overall morbidity and mortality, often incrementally, rather than whether they provide the best possible

[32] S. Lenton and E. Single, "The Definition of Harm Reduction," *Drug and Alcohol Review* 17/2 (1998), 213–20.

[33] UK Harm Reduction Alliance, "Ukhra, Definition of Harm Reduction 2005. Available at <http://www.ukhra.org/harm_reduction_definition.html>.

response. Further, as defined here, harm reduction research often will be testing modifications of existing approaches. As such, they build on the proof of concept demonstrated by earlier studies. Further, they often will be proposed because the "best" intervention—proven in concept to be effective—is not reaching target populations due to its expense or technical complexity. According to this definition, both the lead and AZT studies are examples of harm reduction research. It is a thesis of this chapter that harm reduction studies can be an important tool of public health but also are far from simple, morally. As such, they ought to be acceptable to conduct only under carefully prescribed conditions.

Harm reduction research, as defined, brings researchers into complex moral terrain. On the one hand, harm reduction research is consistent with what public health professionals do routinely: provide interventions to those who bear the burden of societal neglect, and devise and test new interventions where appropriate ones do not exist. In practice, however, harm reduction research is further asking public health researchers to develop and test interventions in situations where effective interventions *do* exist. The problem is one of access, not one of science and technology.

This paradox of course is not new to public health. The evidence is overwhelming that clean water, existing vaccines, and better nutrition would improve global public health outcomes more dramatically than most new technologies currently under investigation. Due to a complex of political, social, and economic structures and policy decisions, much of the world does not have safe water or adequate nutrition, however, and many global clinics have shortages of even the cheapest vaccines and antibiotics. That public health researchers, in response, have developed and tested "second-level" interventions such as bed nets, oral rehydration, and micronutrient supplements is generally thought of not only as laudable, but indeed among the greatest success stories of global public health research.[34] Indeed,

[34] A. Sommer, "Vitamin A Deficiency and the Global Response," *Forum of Nutrition*, 56 (2003), 33–5; H. W. Choi, J. G. Breman, S. M. Teutsch, S. Liu, A. W. Hightower, and J. D. Sexton, "The Effectiveness of Insecticide-Impregnated Bed Nets in Reducing Cases of Malaria Infection: A Meta-Analysis of Published Results," *American Journal of Tropical Medicine and Hygiene*, 52/5 (1995), 377–82; C. C. Carpenter, "The Erratic Evolution of Cholera Therapy: From Folklore to Science," *Clinical Therapeutics*, 12 (Suppl A) (1990), 22–7; "Water with Sugar and Salt," *Lancet* 2/8084 (1978), 300–1.

much of the work of public health has been to identify, test, and implement strategies to reduce disease burden in settings where, if different global or local policies existed to address the larger issues, much of the public health burden would disappear. On the one hand, it is consistent with the ethos of public health to identify opportunities to help now, quickly, and effectively in order to reduce morbidity and mortality. On the other hand, there ought to be moral pause if public health research becomes too willing to accept the problems caused by unjust structures as a given, and works simply to defuse their harmful effects. Public health researchers, then, without thoughtful attention, might well be accused of simply endorsing existing and unjust structures rather than using their considerable talents to change them.

Further, harm reduction as a tool of research raises additional questions that harm reduction in public health practice does not. Presumably, few will advocate that direct aid in terms of food, antibiotics, or physical protection should be denied to people who desperately need so very much more. In practice, one must help those in need in any way possible, regardless of the root causes of their desperate circumstances. In research, however, one cannot promise that one's interventions are providing direct and tangible benefit. Some experimental interventions fail, and sometimes subjects are enrolled as controls. Research is like playing the lottery, and the wager is for a possible, rather than certain, harm reduction payoff, often to future and unspecified "others." Perhaps most importantly, even where research demonstrates the efficacy of the harm reduction interventions, there still is rarely a guarantee that even these simpler harm reduction strategies will be implemented into practice where they are needed, especially given the track record of societal neglect.

It is our thesis that the ethical acceptability of harm reduction as a tool for public health research depends on the ability of a given study to be acceptable according to a series of threshold considerations. These threshold considerations are designed to help researchers and reviewers determine whether the expected benefits from a "harm reduction study" outweigh the inherent problems harm reduction research inevitably raises. (Stated in the reverse, is more harm likely to result from conducting the study or from not conducting it?) Calling the below "threshold considerations" may be overreaching. It is not our belief that all of the listed considerations must be met for a given study to be acceptable. At the same time, the criteria by which to determine if a public health prevention research is

acceptable may be somewhat different from the traditional criteria used on a research ethics checklist. For that reason, they are delineated and explained here.

Further, not only is it true that all criteria are not likely to be met every time, it is also true that conducting a harm reduction study, even one that does meet a threshold level of considerations, will remain morally troubling. When one is trying to make small inroads to considerable social and political injustice, one ought to be troubled by the considerable harm that individual "subjects" continue to encounter, even in the context of their study participation. A relevant, although far from determinative, question is whether more harm is likely to result to individuals and communities involved in harm reduction research from enrolling, or from the study never being done. Deciding whether to approve or conduct such a study must be rational and well-reasoned, but it is unrealistic to believe it will feel completely "right." It is because of the moral tension that will remain after a determination is made that each evaluation must be based on rigorous analysis to determine whether the research, on balance, is acceptable to go forward.

IV. Evaluation Criteria

1. How Inaccessible, Really, is the "Gold Standard" Intervention?

While innumerable effective interventions are out of reach of people who need them, they vary in just how far out of reach they are. This distance can be relevant to how acceptable it is to move forward with testing an alternative strategy that may be of unproven efficacy. There are clear examples of effective "gold standard" interventions (including HIV therapy for many of the global poor) that recently were considered completely inaccessible and now are more widely available. Access, thus, is a moving target, and the reasons for the lack of access vary in morally relevant ways. There is a tremendous difference, practically and morally, between the gold standard intervention being clean water for a large population and a drug recommended by WHO and available currently only to the urban but not rural residents of a poor country. While

there is no clear line that can be drawn to delineate which interventions are too large, complex, or expensive to hold out for, the point of this consideration is to remind researchers that the fact that existing interventions are not available is not enough to consider harm reduction research acceptable in and of itself. Just how inaccessible they are is morally relevant.

2. What is the Researcher's Track Record in Getting Previous Research Interventions Implemented into Practice?

The modal type of harm reduction study, as defined here, is a study to examine the efficacy of a modification to an intervention that has become standard in more affluent settings. Further, as defined here, it is often a preventive intervention designed to reduce morbidity or mortality of an important public health program locally. The need to study the efficacy of the modification is justified, generally, by the claim that the modified strategy will have a better chance of being accessed by the local population than the gold standard has. While such a claim surely sounds sensible, it must be examined and challenged. One might reasonably *assume* that cheaper or simpler interventions will have a better chance of being implemented, but the logic of that assumption alone is insufficient justification. Instead, the track record of the individual researcher, collaborative group, research institution, sponsor, or local community/country of getting research findings implemented into practice should be examined, especially in the setting in which the research is proposed. If this research group has conducted eight studies previously, with spectacular findings, but, sadly, none has been implemented (often through no fault of their own), there is little reason to suspect this next study will be the one to reverse the trend. If, on the other hand, after previous studies by this team or organization, policy changes occurred and interventions were implemented, the practical justification for the compromise approach has more credibility. If communities feel they have experienced public health improvements thanks to this research team, they, and review boards, are more likely to believe public health benefit can be expected from these researchers again. Fortunately, there are innumerable examples of research being conducted in poor

communities that resulted in real change and health improvement for the local community.[35]

3. What Other Evidence Suggests the "Harm Reduction" Intervention, if Effective, might Reach the Community in the Future?

While the best evidence for future implementation may be the track record of the research group, several other factors are relevant and meaningful. A commitment or strong interest from a donor organization or a request for this kind of research from a local official also can add credibility to the researchers' claim that this compromise approach will result in access to the benefit in question.

4. Is the Study itself Likely to Provide Benefit to the Individuals Enrolled and/or to the Study Community?

This consideration asks about any potential benefits from the study, separate from potential future access to the study intervention itself. In general, the greater the degree of compromise from an existing gold standard, and the greater the uncertainty about either efficacy or future access, the more tangible must be the "real time" benefit to individuals and/or the community involved. This is not to say that providing tangible benefit to communities during a study eliminates the need to attend to the previous criteria; to reiterate, *the most important consideration is the likelihood that the harm reduction strategy will be implemented in the future*. At the same time, because both efficacy and future implementation vary in their likelihood, and never can be guaranteed, and because the population is vulnerable to exploitation, other benefits should exist.

For individual participants, if the study indeed is testing a modification of efficacious interventions (rather than completely novel concepts), there may be reason to believe enrollment is beneficial. Reviewers or

[35] R. Levine et al., *Millions Saved: Proven Successes in Global Health* (Washington, DC: Center for Global Development, 2004).

IRBs should examine how much is already known about this category of interventions and make their best determination. Some studies, also, provide ancillary benefits (in terms of other available health care, etc.), again, suggesting that benefit is likely for the individuals who enroll. Ancillary benefits also can exist for communities, and can be morally relevant when weighing the appropriateness of a "harm reduction" study proposal. Capacity development, in terms of improvement of clinic facilities, training of personnel, or improving the water supply, all can provide important benefit. Local input will be needed to determine what types of benefits are meaningful, and negotiations will be needed to determine what researchers and sponsors reasonably can provide. Individual and community benefits should be examined independently. In the end, like with all of the considerations listed here, if one cannot be met, the requirements to meet an adequate standard for the remaining considerations become even stronger.

5. How Susceptible is the Community to Exploitation, and What Safeguards are in Place to Minimize that Risk?

By no coincidence, the very regions of this country and the world with the greatest public health problems also are the regions most susceptible to human rights violations and exploitation.[36] Such communities have the fewest alternatives, the greatest needs, often include individuals with the least education, and, perhaps internationally more than in Baltimore, may have an unquestioning trust of the medical and/or research establishment.[37] The more vulnerable a group is to exploitation or to unexamined acceptance of options presented to them, the greater the burden on researchers to guard against exploitation. This can include involvement of more empowered surrogates—individuals or groups who can speak to the interests of target populations[38]—and it can involve extra scrutiny on the part of review

[36] J. M. Mann, L. Gostin, S. Gruskin, T. Brennan, Z. Lazzarini, and H. V. Fineberg, "Health and Human Rights," *Health and Human Rights*, 1/1 (1994), 6–23.

[37] UNAIDS. "Ethical Considerations in HIV Preventive Vaccine Research" (2004), available at <http://www.unaids.org>.

[38] C. Beyrer and N. Kass, "Human rights, Politics, and Reviews of Research Ethics," *Lancet*, 360 (2002), 246–51.

boards, as always is given to research with vulnerable groups, to ensure that risks are reasonable and benefit guaranteed. When groups are vulnerable, one cannot rely on informed consent as a safeguard to what is acceptable research. Oversight must be vigilant, and it must be mindful that research ethics demands greater protections for subjects and communities when subjects and communities cannot as readily advocate for themselves.

6. What Procedures are in Place to Solve this Dilemma? Is there "Procedural Justice"?

Harm reduction studies are, by definition, morally dilemmatic: there are moral demands to conduct a harm reduction study and moral demands never to compromise, especially when the compromises are only proposed for interventions with the poor. Ultimately, there must be fair procedures in place to balance a need for public health progress against the potential for exploitation and expediency. The degree to which studies have satisfied the above criteria will be a matter of opinion, and which criteria are given greatest weight and whose opinion counts will become determinative. Clearly, affected communities must figure prominently in procedures for making a decision about whether a particular study of this sort should be conducted. A significant responsibility of researchers, in turn, may be to enhance communities' capacity over time to understand research designs, the epidemiology of local health problems, and ethics. One recent initiative of the NIH has that as its goal: designing mechanisms to empower communities regarding how, ethically, public health prevention research should be conducted.[39] At the very least, dialogue between researchers and communities helps educate communities about the importance of certain public health issues and helps inform researchers about the priorities and social context of participants. An informed and involved community will ask tough questions, and ultimately, if they sign on to a harm reduction study, can be the researchers' strongest partner. Through their involvement, they may more fully appreciate the injustice of being offered a second-tier

[39] National Institutes of Health. Environmental Justice: Partnerships for Communication. ES–03–007. 2003. National Institute of Environmental Health Sciences; National Institute for Occupational Safety and Health. Ref Type: Report.

approach which may lead to outrage, and communities or individuals may begin to advocate in a way they never have before. Or perhaps they will decide that, after decades of inaction, they would like the information a study can provide them so they can take action into their own hands. In Baltimore, for example, community meetings can be held in which researchers present the relevant facts: homes are filled with lead; abatement strategies exist but cost $12,000; the government continues to do nothing about it; and landlords have free license to rent lead-filled homes to families with young children, year after year. One option, the researchers can explain, is to study the effectiveness of the various *parts* of a comprehensive abatement strategy, to see which of the pieces makes the most difference, and how much each of those costs. Families, then, might be able to implement key strategies themselves or could advocate to require landlords to implement the most effective pieces. Families, alternatively, through the process of being informed, might reject such a compromise approach as offensive to them as poorer citizens, and might organize advocacy efforts and protests to get public policy changed. Or they might decide to do both. This decision affects them more than anyone; they are, indeed, the "subjects" of such a decision and, as such, their input is critical. However, while the importance of community assessment is clear, it is also critical to remember that community endorsement alone does not make a study ethically acceptable.

7. Are Researchers Engaged in any Activities to Address the Underlying Problem?

When harm reduction is implemented in public health *practice,* attempts generally are made to mediate against the underlying problem as well as to provide practical help through the harm reduction program. Thus, needle exchange programs also direct addicts to drug treatment, and condom distribution programs counsel teens about the advantages of postponing sex. Researchers, too, have a responsibility to advocate for policy changes to eliminate the need for harm reduction approaches. Lead researchers must advocate for access to existing abatement strategies, and HIV researchers must advocate for creative means of financing and distributing proven interventions for HIV. That there may be a practical need to find less expensive or simpler interventions does not relieve professionals of the

responsibility to advocate for access to better services and treatments. Demonstration that researchers have commitments to alleviate the larger problems may, too, be a consideration in determining the acceptability of the harm reduction study. In the end, it may be relevant whether the researcher is committed to reducing the public health problem, writ large, or whether it seems the researcher is interested more narrowly in this particular scientific question.

V. Criticisms of the Harm Reduction Approach in Research

We are aware that the harm reduction research approach and the considerations used, together, to judge the acceptability of such an approach are likely to be criticized. We anticipate here four general areas of criticism and try to respond to them.

1. These Criteria are too Permissive and will Perpetuate Existing Injustices

Interventions for the health problems in question already exist. It is not necessary to test new interventions, particularly interventions expected to be less effective. It both delays communities' access to the proven interventions, and it confirms that the global community is willing to provide the poor with substandard levels of care. If public health professionals are troubled that existing interventions are not reaching communities that need them, then these professionals ought to devote their considerable experience and expertise to advocating for policy change, not for conducting more research. A few public health "crusaders" remind us that compromise vs. wait and see are not the only choices, even in the poorest of communities. Dr. Paul Farmer found a way to raise private funds and bring HIV treatment to poor Haitians when everyone else was debating which compromise approach was most appropriate.[40] Such actions not only provide drugs to people

[40] P. Farmer, F. Leandre, J. S. Mukherjee, M. Claude, P. Nevil, M. C. Smith-Fawzi, S. P. Koenig, A. Castro, M. C. Becerra, J. Sachs, A. Attaran, and J. Y. Kim, "Community-Based

in need, they also serve as individual demonstration projects that other alternatives exist.

From our perspective, this is the most important criticism, and one with significant moral merit. In the end, multiple and varied solutions are needed to make inroads to growing global injustice. Providing short-term help to people who need it is morally required; testing new ideas that may be locally relevant also is required, assuming the above considerations are addressed. The judge in the Grimes Baltimore lead case suggested the researchers should have moved residents to neighborhoods where lead is not a problem. While this seems unreasonable, it also is not reasonable for public health researchers, in situations where inequity is responsible for access problems, to view themselves simply as technical experts. In the end, it is our view that multiple strategies are both needed and appropriate, but the moral tension at stake in this criticism is exactly the tension that causes this context to be so troubling.

2. This Approach is too Strict—Requiring Evidence of Future Access will Make the Best the Enemy of the Good

The considerations above emphasize the need to examine whether it seems likely that the modified intervention actually *will* reach target communities better than the "gold standard" intervention did. This criticism agrees that future access, of course, is the primary goal of conducting the research, but that it is unrealistic to demand some assurance of that before the study starts. Most public health interventions used today were tested merely as good ideas, with no guarantees of future implementation when first tested. When results of important studies, for example with Vitamin A or nevirapine, showed dramatic public health improvement, it was then easier to convince health ministers and donors to commit resources for implementation. Most donors and government officials will *not* commit to future funding, and such a criterion may result in many good ideas never being tested, and enormous potential will be lost.

Approaches to HIV Treatment in Resource-Poor Settings," *Lancet* 358/9279 (2001), 404–9; P. Farmer, F. Leandre, J. Mukherjee, R. Gupta, L. Tarter, and J. Y. Kim, "Community-Based Treatment of Advanced HIV Disease: Introducing Dot-Haart (Directly Observed Therapy with Highly Active Antiretroviral Therapy)," *Bulletin of the World Health Organization*, 79/12 (2001), 1145–51.

This, too, is a significant criticism. We have two responses. First, the considerations listed above are meant to be examined and weighed in totality. There may be more weight for one and less weight for another. In the end, individual judgments must be made about study acceptability. The point of listing them is to identify *which* factors are morally relevant to allowing such types of research to go forward. Saying that the modified intervention is less expensive or simpler is *not* enough to justify the study being done. Instead, there must be some reason to believe that the simpler intervention will be accepted. The "evidence" for future implementation is unlikely to be a firm "contract" as has been suggested by some as that, indeed, seems unrealistic.[41] Rather, it may be that the funder has a track record for policy advocacy or the research team has been collaborating with the local community enough to have a track record of change. Second, and most important, examining the likelihood of future access is not meant to apply necessarily to all research conducted in poor communities. Rather, it is listed here as a critical consideration for research pervaded by a very particular type of moral problem: there is an existing public health intervention that could be provided within the local community were there a different level or type of political will, and the study in question is a direct response to that lack of political will. Thus the explicit rationale for the study is to find interventions that have a chance of being more *accessible* to poor communities, by virtue of their being less expensive or less complex. When the justification for engaging in harm reduction research is based almost exclusively on the better likelihood of future access (not simply on efficacy), then demonstration of likelihood of future access must enter the equation.

3. This Approach is too Strict—Few Studies have Results that, on their own, are Ready to be Implemented as Policy

To assume that one study will have results so conclusive as to change public policy shows ignorance of both science and policy making. Replication of studies is a core feature of scientific truth, and to suggest that an intervention

[41] A. K. Page, "Prior Agreements in International Clinical Trials: Ensuring the Benefits of Research to Developing Countries," *Yale Journal of Health Policy, Law, and Ethics*, 3/1 (2002), 35–64.

should be guaranteed future access suggests that public health programs may be implemented—presumably at great cost—with insufficient scientific validity.

In response, of course policy only should be implemented when the evidence for effectiveness is solid. Discussions of future access only are relevant for interventions that have either extraordinarily dramatic results and/or interventions whose effectiveness has been validated in several studies. At the same time, when testing a modification of an existing intervention, there may be less need to replicate multiple times than when testing a truly novel concept. Both the lead and the HIV studies tested components of effective, more complex regimens. Thus the total trajectory between idea and results likely will be shorter. We acknowledge that not all harm reduction research literally will be testing modifications of existing approaches. Some harm reduction research will be testing a more novel approach, and those studies will have a higher bar to pass in terms of concluding about effectiveness. Decisions will need to be decided on a case by case basis, but the considerations for acceptability will be the same: what is the track record of investigators in getting study interventions available to communities when research is over? What related benefits are provided along the way? And how out of reach is the "gold standard" intervention?

4. This Approach is too Strict—If a Study Provides Benefits, it should Simply be Provided to People who are in Need

It is likely true that the houses inhabited by participants in the Baltimore lead study put residents at lower risk of lead poisoning than other dwellings in which they would have lived, since all houses received some abatement, and every family received education about lead poisoning prevention. Similarly, the women in the short-course AZT trials likely received better care and, in some cases, a lower risk of having a baby infected with HIV, by virtue of being in the trials. That individual studies provide benefit to those who enroll in them is not the only relevant ethics consideration, however. Studies that provide benefit to the individuals who enroll can still be exploitive.

What is complicated about research is that its ultimate goal is not to provide service. Rather, its goal is to make public health *change* based on

scientific discovery. Since many studies do not *yet,* or do not *alone,* precipitate policy change, it is relevant and useful to provide benefit to study subjects. At the same time, to begin to confuse research and service purpose by placing too much emphasis on the benefits that are provided during the study itself *without attention* to how the study is relevant and can be part of a trajectory of public health policy change is disingenuous to the purpose of research and, in turn, to research ethics. In our saying that improving the well-being of study subjects is not enough to ethically justify a study in a poor region is not to suggest that benefits be taken away from people who desperately need them. Rather, it is to continue to push to change the norm, as necessary, by increasingly viewing research as a long-term engagement with a community, rather than a short-term treatment program. If there is no evidence that research programs lead to public health benefit among anyone beyond the individuals who took part in the study, the research enterprise clearly is failing. Fortunately, there are many examples of research collaborations leading to public health practice changes in the community, as a direct result of the research.[42]

5. Requiring Local Input to Sort out These Dilemmatic Situations is Unrealistic

Often local communities do not understand these larger issues, or they simply are attracted to the economic or employment benefits of a study coming to their community; local researchers, too, may have conflicts, given the professional and economic benefits they may reap through involvement in the research.

While these criticisms are legitimate in some settings, the change in what many local communities understand about research today compared to even ten years ago is extraordinary, in terms of having more individuals with a sophisticated understanding of research, and of why research is conducted. With appropriate capacity development and simply with more experience with research, important changes have occurred in the ability of local groups

[42] L. J. Fiedler, "The Nepal National Vitamin A Program: Prototype to Emulate or Donor Enclave?," *Health Policy and Planning*, 15/2 (2001), 145–56; F. Nyonator, J. K. Awoonor-Williams, J. Phillips, T. Jones, and R. Miller, "The Ghana Community-Based Health Planning and Services Initiative for Scaling up Service Delivery Information," *Health Policy and Planning*, 20/1 (2005), 25–34.

to advocate for themselves, and to advocate with sophistication. Ultimately, however, some local groups will not be sufficiently informed or empowered to be their own best advocate. This does not diminish our attempts to empower them, or to try to involve them where we can. Input occurs along a spectrum, not as a yes or no event. Groups can articulate what is important to them, even without understanding the specifics of a study. They can be told that there are some very expensive medicines they can fight to get, and they can also decide to figure out if other interventions also might be helpful in the meantime. The responsibility is ours to begin to frame the dilemmas as they really exist and get legitimate input about how to resolve them. That injustice in distribution will not be new to the communities in question. Framing the issues as they exist, ultimately, is respectful of communities involved, and can add some important voice to how research should be redesigned and when it is acceptable to go forward.

Conclusion

Many ethical landmines can exist in the conduct of public health research, and many exist even when focusing more narrowly on research across economic and/or cultural divides. The purpose here was to examine a still more specific situation: when, if ever, can it be ethically acceptable to conduct research to find simpler or cheaper public health preventive interventions than those already proven to be efficacious?

Harm reduction research is offered here as a morally acceptable approach, but one that only can be undertaken when there are good reasons to believe that the intervention (often a modification of existing approaches) will be effective and good reasons to believe that the intervention will reach those who need it. Harm reduction research will be troubling on many levels. Working within the confines of extreme injustice, one must walk a fine line between improving the situation and condoning it. How can public health professionals endorse seeming band-aid solutions for people who need so very much more? At the same time, after decades of observing little progress on the larger issues, public health professionals, whose mandate is to reduce morbidity and mortality among the public, may seek additional tools. The ultimate test of the acceptability of such an approach is indeed

its ability to demonstrate a tangible reduction in public health harm, particularly over the long run. Yet, in the short run, this will always be uncertain, because one cannot anticipate if the intervention will be effective, and because, given a history of failing to implement other interventions, guarantees of implementation of simpler or cheaper interventions are hard to secure.

When involving the world's poorest and most vulnerable populations, the ethical stakes are higher. We owe it to these individuals as well as to the integrity of our own profession to create and abide by strict but reasonable standards for harm reduction research in public health. A reduction of public health harm must be ensured for those who have received fewer global benefits than clearly is their due.

Global Bioethics

Issues of Conscience for the Twenty-First Century

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