



THE SOCIAL VALUE OF HEALTH RESEARCH AND THE WORST OFF

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Keywords

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ABSTRACT

In this article we argue that the social value of health research should be conceptualized as a function of both the expected benefits of the research and the priority that the beneficiaries deserve. People deserve greater priority the worse off they are. This conception of social value can be applied for at least two important purposes: (1) in health research priority setting when research funders, policy-makers, or researchers decide between alternative research projects; and (2) in evaluating the ethics of proposed research proposals when research ethics committees (RECs) assess whether the social value of the research is sufficient to justify the risks and burdens to research participants and others. In assessing how far a proposed research project will advance the interests of people who are more disadvantaged, research priority setters and RECs should examine (at least) the diseases that the research targets and the type of research. Just as certain diseases impose a greater burden on people who are more disadvantaged, so certain types of intervention and forms of research are more likely to benefit people who are more disadvantaged. We outline which populations are likely to be representative of the global worst off and identify what types of health research, and which disease categories, are priorities for these populations.

1. INTRODUCTION

Current global health research spending is skewed towards the smaller disease burden in high-income countries.¹ Many of the health needs of the global worst off do not attract attention among high-income country researchers who produce the vast majority of global health knowledge, largely in response to their own local needs.² This raises concern about the paucity of health knowledge relevant to poor populations.

Ethical analysis relating to the beneficiaries of the results of health research is concerned with the *social value* of that research. The social value of research is important for two different sets of decision-makers. First, those who evaluate the ethics of proposed research

studies, such as the research ethics committees (RECs)³ who are charged with protecting the rights and well-being of research participants and their communities. Research that imposes risks and burdens on participants or communities is generally thought to be justified only when it has sufficient social value. Second, those who make decisions about which research to pursue: health research *funders* (public or private) who sponsor health research, health research *policy makers* who set local, national and global health research priorities, and *researchers* who make decisions about what scientific topics to pursue. The resources available for global health research are not nearly sufficient to support all the valuable projects that could be pursued, which makes difficult decisions about which research to conduct

¹ *Global health research* refers to health research worldwide.

² J. Evans, J. Shim & J. Loannidis. Attention to local health burden and the global disparity of health research. *PLoS ONE* 2014; 9(4): e90147.

³ A research ethics committee (REC) is also known as an institutional review board (IRB), an independent ethics committee (IEC), ethical review board (ERB), or research ethics board (REB).

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Joseph Millum Disclaimer: The views expressed are the author's own. They do not represent the position or policy of the National Institutes of Health, US Public Health Service, or the Department of Health and Human Services.

unavoidable. All else being equal, across the global health research landscape, health research with greater social value should be preferred.

In this article, we argue that the social value of health research should be conceptualized as a function of both the expected benefits of the research project and the priority that the beneficiaries deserve. People deserve greater priority the worse off they are. We begin by explaining what role we think social value should play in research ethics and in priority setting for health research. We then argue in favour of our conception of social value and set out a specific account of disadvantage that is helpful in operationalizing that conception. Finally, we argue that the research with the highest social value generally focuses on ways to alleviate the diseases that most burden the worst off. This can be achieved through the development of products appropriate for low-income settings, and by implementation and health systems research in resource-poor health systems. We close by responding to objections.

2. THE RELEVANCE OF SOCIAL VALUE TO HEALTH RESEARCH

The idea that to be ethical, research must be socially valuable is widely accepted in medical ethics.⁴ The social value benchmark requires that society (or the field of health) should gain important generalizable knowledge from the research. In the words of the Nuremberg Code, ‘The experiment should be such as to yield fruitful results for the good of society.’⁵ Alan Wertheimer clarifies that, ‘On a *de minimis* account, virtually all research will have *some* social value and the social value requirement would be too easy to satisfy. So it is best to understand the social value requirement as requiring *significant* social value.’⁶

Multiple justifications for the social value requirement have been proposed. Some authors suggest that the justification includes the need to maintain ‘public confidence in the research endeavor’ – that the enterprise of research

relies on a ‘credible social assurance’ that research advances the common good.⁷ In particular, the willingness of society to support funding for research and the willingness of prospective participants to participate in research depend on a generalized social trust that research is worthy, i.e. that members of the research community are collaborating in a way that advances the common good.⁸ An alternative justification for why social value is an ethical requirement is the responsible use of finite societal resources. Research resources are limited; assuming that it is possible to compare the relative value of different research studies, research that is likely to generate greater improvements in health or well-being is of higher social value and so should be preferred to less socially valuable research, all else being equal. It may even be considered unethical to devote scarce societal research resources to research of low social value, because those resources might be deployed in support of more valuable research.⁹ Finally, the social value of a research project must be sufficient to justify the risks and burdens of the research for research participants and the communities from which they are recruited. For example, it may be judged unethical to engage in research that poses net risks to participants unless those risks are justified by the importance of the knowledge that results.

It is worth noting that RECs who are evaluating whether a research study has sufficient social value may have to take more than just global social value into account. Some commentators argue that the populations that host research also ought to benefit from the results of the research, particularly when those populations are disadvantaged in other ways.¹⁰ This suggests that the amount of *local* social value may be relevant to justifying research, not just the amount of global social value. Although we do not have the space to address this issue

⁴ E. Emanuel, D. Wendler & C. Grady. What makes clinical research ethical. *JAMA* 2000; 283: 2701–11; Council for International Organizations of Medical Science (CIOMS). *International Ethical Guidelines for Biomedical Research Involving Human Subjects*. Geneva, Switzerland: Council for International Organizations of Medical Sciences (CIOMS) and World Health Organisation (WHO); 2002; The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*. Elkridge, USA: National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research; 1979; World Medical Association (WMA). *Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects*. Fortaleza, Brazil: 64th WMA General Assembly; 2013.

⁵ The Nuremberg Code. *JAMA* 1996; 276.

⁶ A. Wertheimer. The social value requirement reconsidered. *Bioethics* 2015; 29: 301–8: 302.

⁷ A. Rid & D. Wendler. A framework for risk-benefit evaluations in biomedical research. *Kennedy Inst Ethics J* 2011; 21: 141–79; A. London. A non-paternalistic model of research oversight: Assessing the benefits of prospective review. *J Law Med Ethics* 2012; 40: 930–44.

⁸ A. London, *Ibid*.

⁹ E. Emanuel, D. Wendler & C. Grady, *op. cit.* note 3.

¹⁰ See for example: A. London. 2008. *Responsiveness to Host Community Health Needs*. In *The Oxford Textbook of Clinical Research Ethics*. E. Emanuel, R. Crouch, C. Grady, et al., eds. New York, USA: Oxford University Press: 737–744; Council for International Organizations of Medical Sciences (CIOMS). 2002. *Guideline 10: Research in populations and communities with limited resources*. In *International Ethical Guidelines For Biomedical Research Involving Human Subjects*. Geneva, Switzerland: Council for International Organizations of Medical Sciences (CIOMS) and World Health Organisation (WHO): 51–53. Available at: http://www.cioms.ch/publications/layout_guide2002.pdf [Accessed 14 Apr 2016]; and World Medical Association (WMA). 2013. *Guideline 20: Vulnerable Groups and Individuals*. In *Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects*. Fortaleza, Brazil: 64th WMA General Assembly: 3–4. Available at: <http://www.wma.net/en/30publications/10policies/b3/index.html> [Accessed 12 Apr 2016].

in the current article, the analysis of social value we give would apply to assessing local social value as well.

Independent of its use as a standard to judge whether a proposed research study is ethical, the concept of social value is relevant to setting priorities for which health research to pursue. If less socially valuable research displaces research that would have been more valuable for the global population, we miss out on important opportunities to address global health priorities. All the decision-makers we identified above – funders, policy makers, and researchers – therefore have some moral reason to take social value into account when deciding what research to pursue.

Exactly how social value fits into the ethics of decision-making for those who are deciding which research to pursue might depend to some extent on the decision-maker. For example, private funders may have more discretion about what research to pursue than government entities.¹¹ A government agency will not only have reason to consider the global social value of the research it supports, in virtue of obligations to the global population, but also special responsibilities that it owes to its citizens or others in the region. Those people may have a greater claim to have their health needs considered than people from other countries. In this article, we do not attempt to answer the complex question of exactly how global social value relates to the other ethical obligations and permissions of those who make decisions about what health research to pursue. We simply provide an analysis of what social value consists in, which each decision-maker can use in the way that they need.

¹¹ A. Wertheimer. *op. cit.* note 5. In 2007 research and development investments by Pharmaceutical Research and Manufacturers of America (PhRMA) member companies totalled US\$44.5 billion. Eighty percent of this (US\$35.4 billion) was invested in domestic research and development. US\$9.1 billion (20%) of investments were spent abroad. See: M. Burke & S. Matlin (eds). 2008. Monitoring Financial Flows for Health Research 2008: Prioritizing research for health equity. Geneva, Switzerland: Global Forum for Health Research. Available at: http://announcementsfiles.cohred.org/gfhr_pub/assoc/s14888e/s14888e.pdf [Accessed: 20 Mar 2016]; While public and philanthropic research funders all strive to improve the health of the global population, it is worth qualifying that the proportional commitment to funding non-national global research priorities varies substantially by funder. In general, bilateral aid agencies and the Gates Foundation direct the majority of their research funding to health needs in LMICs. The Wellcome Trust and NIH allocate a smaller minority of their research funding to global research; the majority focuses on national research priorities. See: E. Dorsey, J. Thompson, M. Carrasco, et al. Financing of U.S. Biomedical Research and New Drug Approvals across Therapeutic Areas. *PLoS ONE* 2009; 4(9): e7015. Available at: <http://www.plosone.org/article/info:doi%2F10.1371%2Fjournal.pone.0007015> [Accessed 20 Mar 2016]; The Global Fund. 2010. The Global Fund Annual Report 2009. Available at: <http://www.theglobalfund.org/en/archive/annualreports/> [Accessed 20 Mar 2016]; and G-Finder. 2009. Neglected Disease Research and Development: New Times, new trends. Available at: <http://www.georgeinstitute.org/g-finder-2009-neglected-disease-research-and-development-how-much-are-we-really-spending> (p.63) [Accessed 20 Mar 2016].

3. SOCIAL VALUE AND DISADVANTAGE

Social value is a matter of the ethical importance of benefits. Paradigmatically, these are health benefits to patients or populations beyond those enrolled in a research study that result from the knowledge the study generates. We can leave open for now exactly which benefits count.¹² Almost everyone believes that the fact that someone benefits from a health-care intervention is a reason in its favour.¹³ It is also commonly believed that we have greater reason to provide someone with a health benefit who is very sick than someone who is only slightly unwell, even if the size of the benefit provided is the same. The idea that the worst off deserve greater priority is widely endorsed in medical ethics and philosophy.¹⁴ It is also supported by studies that suggest that people regard health improvements of the same size as substantially more important when the beneficiaries are worse off.¹⁵ On the basis of these widespread views, we endorse a moderate prioritarian approach to resource allocation according to which ‘the worst off deserve substantial, though not absolute, priority’.¹⁶ Applied to the context of research, this suggests that the social value of research should be conceptualized as a function of two considerations: 1) the expected benefits of the research project; and 2) the degree of disadvantage of the expected beneficiaries of the research project. The more benefit that is anticipated from a research project, the higher its social value; the more disadvantaged the beneficiaries of a research project, the higher its social value.

A moderate prioritarian conception of social value supports the view that, all else being equal, the research with the greatest social value will be research that offers the greatest benefit to the global worst off.¹⁷ For those who are evaluating the ethics of proposed research studies, this implies that research that targets the needs of the worst off will be easier to justify. For those who are

¹² As we discussed in Section 2, some authors (including ourselves) believe that it can be important whether social value is *local*. We think this is orthogonal to our point in the present paper, but we do not mean our argument to imply that research can be justified just in virtue of it having a sufficient *amount* of social value.

¹³ That does not make it ethically permissible or required, *all things considered*, to provide someone a benefit. For example, someone else might have a prior claim to the resource that would make it all things considered wrongful to provide the resource to the original beneficiary.

¹⁴ D. Sharp & J. Millum. The post-2015 development agenda: keeping our focus on the worst off. *Am J Trop Med Hyg* 2015; 92: 1087–9.

¹⁵ K. Shah. Severity of illness and priority setting in healthcare: a review of the literature. *Health Policy* 2009; 93: 77–84.

¹⁶ D. Sharp & J. Millum. Prioritarianism for global health investments: Identifying the worst off. *J Appl Philos* 2015; DOI: [10.1111/japp.12142](https://doi.org/10.1111/japp.12142): p. 2.

¹⁷ All else may not be equal, since there may be cases in which much more benefit can be provided to a group that is badly off, but not the very worst off. We consider this possibility in Section 6 when we respond to objections.

engaged in setting priorities for research, this implies that they should look first to the knowledge that is needed to benefit the worst off.

Moreover, even those who do not have prioritarian views about the moral importance of benefits have good reason to think that prioritizing the worst off usually has the greatest value. Three ethical principles are widely cited in the context of allocating scarce resources: the utilitarian principle, which entails maximizing total benefits; the egalitarian principle, which supports increasing equality; and the prioritarian principle, which promotes giving greater priority to those who are worse off. Prioritizing the worst off will be optimal most of the time according to all of these principles because in most cases it also serves to maximize total health benefits and increase global equality. The research needed for diseases which kill poor young people in low- and middle-income countries (LMICs) is likely to provide large gains in health and well-being for the money invested in them. These are diseases that are common and have a huge effect on the health of people who suffer from them. As our examples below suggest, research on these conditions and the research products that arise from it are likely to be low-cost in comparison with a great deal of the resource-intensive clinical trials that take place in high-income settings. Investing in the cost-effective health research most needed by the worst off is therefore likely to maximize total benefit, promoting the utilitarian principle of health maximization. The types of health research needed in the world's worst off populations are also targeted at those populations with the lowest life expectancies. Variation in life expectancy is a marker for inequality in health. Allocating scarce health research resources to those with the lowest life expectancy has the prospect of narrowing the gap in global life expectancies, thereby increasing global health equality.

In global health research, therefore, as in other spheres in which we are concerned with the well-being of very disadvantaged people, the differences between what competing theories of fair allocation recommend in practice are minimal. As Jonathan Wolff and Avner De-Shalit argue, the dominant views in moral and political philosophy tend to converge:

[P]rovided that there are people in a society who have not yet achieved sufficiency, and provided that we have in mind limited, or at least finite, budgets and financial resources, then all of these views appear to converge on the same general policy prescription in the short to medium term: identify the worst off and take appropriate steps so that their position can be improved.¹⁸

¹⁸ J. Wolff & A. De-Shalit. *Disadvantage*. Oxford, United Kingdom: Oxford University Press; 2012. p. 3–4.

4. HOW HEALTH RESEARCH CAN PRIORITIZE THE WORST OFF

If we accept that the health research with the highest social value will normally prioritize the worst off, then three further questions must be answered. First, we need to know who the worst off are. Second, we need to identify the diseases and conditions that most affect the worst off. This is particularly important given that global health research spending is currently skewed towards the smaller disease burden in high-income settings. Third, we need to ensure that the *types* of research prioritized on the global health research agenda are those that are relevant to the needs of, and so likely to benefit, the worst off. Prioritizing research on the diseases that most affect the worst off is helpful in maximizing social value; however, we will argue that it is not sufficient.

Note that we do not here take a position on the optimal process for setting priorities for research that benefits the worst off. For example, we do not endorse a pathway of global priority-setting that has priorities being set by disease category *prior* to priorities being set for different types of research. This would probably contribute to further fragmentation of non-disease specific forms of research, such as health systems research, that are needed to achieve public health and equity across countries.¹⁹ Neither do we take a position on the relative weight that ought to be assigned to disease-specific health research versus other forms of cross-cutting health research. We are simply underscoring the importance of taking into account both 1) *magnitude and cause* of disease burden, and 2) *type* of research when prioritizing health research relevant to the worst off.

Who are the worst off?

Before we can identify the diseases and conditions that affect the worst off, we must first identify who the global worst off are. This article adopts Sharp and Millum's *total advantage* view according to which: 1) 'the worst off are those who have the greatest total lifetime disadvantage', not just those who are in a bad situation at the present time; 2) 'advantage foregone due to premature death should be treated in the same way as other ways of being disadvantaged at a time', i.e. how well a person's overall life goes is a function of both the quality and the length of her life; 3) 'how badly off someone is depends on the actual outcomes that will befall her without intervention, not her prospects at a time'; and 4) 'all significant forms of disadvantage count for determining who is worst off, not just disadvantage relating to health', i.e. factors other than a person's health

¹⁹ See M. Ranson & S. Bennett. Priority setting and health policy and systems research. *Health Res Policy Syst* 2009; 7: 27.

condition, including economic poverty, poor access to education, and the violation of civil and political rights, can affect how badly off someone is.²⁰ For the purposes of this article, features 1), 2), and 4) are most important. We briefly motivate them here before assessing which people constitute the worst off under this conception of disadvantage.²¹

Treating disadvantage as a matter of how someone fares over their lifetime, not just at the current time, helps make sense of a number of other normative judgments. It explains why it can be reasonable to make a sacrifice now in order to benefit later (for example, someone may quite reasonably choose to work harder at an unpleasant job now in order to enjoy a more comfortable retirement later). It also explains why it makes sense to compensate someone for harms that they experienced in the past. The notion that a shorter life is worse than a longer one, all else being equal, is highly intuitive. The fact that people are frequently willing to trade off quality against quantity of life also suggests that both are relevant to assessing someone's degree of disadvantage. Finally, there has been substantial debate about whether health policy-makers should care only about health or about other aspects of well-being also. We find views that accord lexical or near-lexical priority to health highly implausible in this context. First, even if there is a reason for those who work in health research to focus on health outcomes, this does not imply that we should identify which people deserve greatest priority just in terms of their health. Second, it is commonly thought that patients, physicians, and policy-makers should take into account more than just health when they make health-care decisions.²² For example, someone may reasonably care more about being able to speak with her family than being free of pain, and one of the primary functions of health insurance is to avoid catastrophic financial losses that may push whole families into poverty.²³ We see no reason why similar considerations would not apply to health research.²⁴

²⁰ D. Sharp & J. Millum. *op. cit.* note 15, pp. 1–2.

²¹ Our arguments here draw on D. Sharp & J. Millum. *op. cit.* note 13 and D. Sharp & J. Millum. *op. cit.* note 15.

²² D. Brock. Separate spheres and indirect benefits. *Cost Effectiveness and Resource Allocation* 2003; 1: 4. Available at: <http://www.resource-allocation.com/content/1/1/4> [Accessed 25 Mar 2015].

²³ K. Xu, D. Evans, G. Carrin, et al. Protecting households from catastrophic health spending. *Health affairs* 2007; 26(4): 972–983.

²⁴ For further argument see D. Sharp & J. Millum *op. cit.* note 15, pp. 8–10. Pluralism about disadvantage is a common view in applied ethics and has been widely endorsed by commentators concerned with the worst off, for example, J. Wolff & A. de-Shalit, *op. cit.* note 17; M. Powers & R. Faden. 2006. *Social justice: the moral foundations of public health and health policy*. New York, USA: Oxford University Press.

According to Sharp and Millum's conception the worst off are those who have the least overall lifetime well-being. They argue that those who die young will therefore be among the worst off. Since the vast majority of young deaths occur in low- and middle-income countries (LMICs) and disproportionately among the poor in these countries, adopting this conception also entails accepting that those who die young *and* are subject to other forms of disadvantage, for example, economic poverty, will be the majority of those who constitute the global worst off.²⁵ Giving priority to the research needs of the worst off would therefore imply that those who die young (children, adolescents and young adults) and live in LMICs deserve the highest priority.

What diseases burden the worst off?

The leading causes of disease and death in younger age groups in LMICs remain communicable diseases, conditions related to childbirth, and nutritional disorders.²⁶ The most important communicable diseases include lower respiratory infections, diarrheal diseases, malaria, meningococcal disease, and HIV/AIDS.²⁷ Further research towards addressing these, as well as the maternal health conditions that affect infant and child mortality, should remain a priority for the global research agenda, even though the total global burden of disease has started to shift towards non-communicable diseases.²⁸

What *types* of research would best address the health needs of the worst off?

We have assumed that research into a particular disease has some prospect of benefiting people with that disease. By implication, if we do almost *any* research on diseases or conditions that are prevalent in the worst off, then that research has some prospect of benefiting the worst off. However, while prioritizing research on the diseases that most affect the worst off is necessary, it is not sufficient. We must also ask if the *types* of research prioritized on the global health research agenda are relevant to the needs of the worst off. Within and across diseases, the types of research

²⁵ T. Houweling & A. Kunst. Socio-economic inequalities in childhood mortality in low- and middle-income countries: a review of the international evidence. *Br Med Bull* 2010; 93: 7–26.

²⁶ Institute for Health Metrics and Evaluation (IHME). 2015. Results. Seattle, WA: IHME. Available at: <http://www.healthdata.org/results> [Accessed 23 Mar 2015].

²⁷ Institute for Health Metrics and Evaluation (IHME). 2015. Data visualisations. Seattle, WA: IHME. Available at: <http://vizhub.healthdata.org/gbd-compare/> [Accessed 30 Oct 2015].

²⁸ N. Barsdorf. 2012. *South Africa's duty to support health research for the global poor*. Dissertation for the degree philosophiae doctor (PhD). Bergen, Norway: University of Bergen.

needed in low-income settings might be different from the types of research that are typically conducted in higher-income settings.²⁹

Focusing on the types of research that are needed to benefit the worst off also heads off possible objections to the idea that research is still warranted in some of these disease areas. Many of the diseases that most burden the worst off globally already have effective treatments or proven preventive interventions. For example, pneumococcal disease is the world's number one vaccine-preventable cause of death among infants and children younger than five years of age. A pneumococcal vaccine able to dramatically reduce the number of children dying was approved in the United States in the year 2000.³⁰ Malaria can be prevented, diagnosed and treated with existing, proven interventions.³¹ Consequently, some might argue that further research is not needed in many of these disease groups. Since we already have cost-effective interventions for many of the diseases that affect the worst off, and these interventions are in use in other parts of the world, it could be argued that it is not more research that we need. However, it does not follow that because interventions exist and are in use in high-income countries, that we have all the information we need in order to provide effective interventions to the populations that need them most. There are particular *types* of health research that are relevant to, and still needed by, the worst off.³²

²⁹ Ibid.

³⁰ T. von Schoen-Angerer. 2009. Statement by Dr. Tido von Schoen-Angerer, Director of the campaign for access to essential medicines, Medecins Sans Frontieres, in response to the G-Finder report. London, England: G-Finder. Available at: http://www.msfaccess.org/media-room/press-releases/press-release-detail/index.html%3ftx_ttnews%5Btt_news%5D=1529&cHash=2d83950e65&no_cache=1&print=1 [Accessed 12 Oct 2010].

³¹ Roll Back Malaria. 2011. Global Malaria Action Plan for a malaria-free world. Geneva, Switzerland: Roll Back Malaria. Available at: <http://www.rollbackmalaria.org/gmap/index.html> [Accessed 27 Jun 2011].

³² Note that for the purposes of this article we adopt a relatively narrow conception of health research as restricted to research on components of the health-care system. It is possible that research on factors outside the health-care system – such as housing or working conditions – could also be highly beneficial to the worst off, but assessing the expected benefits of research on the social determinants of health lies beyond our expertise. Funders with the flexibility to support research with a broader scope could still apply our conception of social value to inform their judgments about which research to fund. For some discussion of the role of research in addressing the social determinants of health, see: CSDH. 2008. Closing the gap in a generation: health equity through action on the social determinants of health. Final Report of the Commission on Social Determinants of Health (CSDH). Geneva, Switzerland: World Health Organization (WHO). Available at: http://www.who.int/social_determinants/thecommission/finalreport/en/ [Accessed 19 Aug 2016].

5. TYPES OF HEALTH RESEARCH MOST NEEDED BY THE WORST OFF

Most child deaths from pneumonia, diarrhoea, malaria and neonatal complications could be prevented using relatively low-cost, proven interventions.³³ Cost-effective integrated approaches to the management of childhood illnesses are available and in use in many parts of the world.

But populations in low-income settings confront a plethora of social constraints and health threats that make the implementation of effective health prevention and treatment programmes particularly difficult. People often have limited knowledge of preventive health practices and inadequate access to good quality healthcare. In addition, health is regularly undercut by other challenges such as inadequate water and sanitation infrastructure, high pathogen loads, and socio-economic obstacles to behaviour change. In low-income settings health systems are underfinanced and undermined by severe health worker shortages. For these reasons it is not always possible to successfully implement and sustain health interventions in many low-income settings.³⁴ They are either unsuitable for those settings (pointing to a need for a product tailored to the setting), their implementation has not been tested in those settings (pointing to the need for implementation research), or they are unable to be adequately integrated into fragmented public health systems (pointing to the need for health systems research).

Thus, there are three types of health research that are most needed to meet the health needs of the worst off, even when there are successful interventions already in use in other parts of the world: 1) Product and intervention research: research directed towards the development of products and interventions appropriate for, or tailored to, low-income settings; 2) implementation research: research directed towards effectively implementing existing appropriate interventions in resource-poor settings; and 3) health systems research: research directed towards addressing fragmented public health systems.³⁵ We consider them in turn.

³³ Ibid; N. Barsdorf, *op. cit.* note 27; B. Bloom, C. Michaud, J. La Montagne, et al. 2006. Chapter 4: Priorities for global research and development interventions. In *Disease control priorities in developing countries* (2nd edn). D. Jamison, J. Breman, A. Measham, et al., eds. New York, NY: Oxford University Press and The World Bank: 103–118.

³⁴ T. Madon, K. Hofman, I. Kupfer et al. Implementation science. *Science* 2007; 318: 1728–9.

³⁵ The definition and boundaries of health systems research are still being debated and defined. Some see implementation research as encompassed within health systems research, whereas others see them as distinctive fields. For definitions of implementation research and health systems research see: J. Remme, T. Adam, F. Becerra-Posada, et al. Defining Research to Improve Health Systems. *PLoS Med* 2010; 7(11): DOI: [10.1371/journal.pmed.1001000](https://doi.org/10.1371/journal.pmed.1001000); S. Hoffman, J. Røttingen, S. Bennett, et al. 2012. Background Paper on Conceptual Issues Related to Health Systems Research to Inform a WHO Global Strategy on Health Systems Research: A Working Paper in Progress. Available at: http://www.who.int/alliance-hpsr/alliancehpsr_backgroundpaperhsrstrat1.pdf [Accessed 19 Mar 2016].

Products and interventions for low-income settings

Disease-specific biomedical research and development is essential for health and includes vector-control products,³⁶ microbicides, vaccines, diagnostics, drugs, interventions, and platform technologies.³⁷ Even when there are successful interventions available and in use in other parts of the world, research and development of products and interventions that are appropriate for, or tailored to, low-income settings is often still warranted.³⁸ Some products that were originally developed for use in high-income countries can be used with relative ease in LMIC settings. Others are inappropriate because they are unaffordable or cannot be used in a setting lacking the hi-tech infrastructure found in higher-income country health facilities. Ten years after the pneumococcal vaccine was approved in the United States, the vaccine remained expensive, was still marketed in a highly unfeasible form, and was still not available in most low-income countries where it could have made the biggest difference in reducing unnecessary deaths.³⁹ Research is needed to develop more affordable or less technology-dependent versions of the same product.

The product gap for LMICs is illustrated by a 2002 study that identified ten promising biotechnologies for improving health in developing countries.⁴⁰ These included, among others, modified molecular technologies for affordable, simple diagnosis of infectious diseases. Accurate and early diagnosis of infectious disease is important not only for prompt treatment, but also to limit the spread of disease. Many diagnostic techniques

³⁶ Examples of vector control products include pesticides, biological control agents and vaccines targeting animal reservoirs.

³⁷ Examples of platform technologies include adjuvants, diagnostic platforms and delivery devices.

³⁸ R. Viergever, R. Terryb & G. Karam. Use of data from registered clinical trials to identify gaps in health research and development. *Bull World Health Organ* 2013; 91: 416–425C. Available at: <http://www.who.int/bulletin/volumes/91/6/12-114454.pdf> [Accessed 14 Mar 2016]; D. Vidyasagar. Global notes: the 10/90 gap disparities in global health research. *Journal of Perinatology* 2006; 26: 55–56. Available at: <http://www.nature.com/jp/journal/v26/n1/full/7211402a.html> [Accessed 14 Mar 2016]; L. Doyal. Gender and the 10/90 gap in health research. *Bull World Health Organ* 2004; 82: 3; W. Moss, G. Darmstadt, D. Marsh, et al. Research priorities for the reduction of perinatal and neonatal morbidity and mortality in developing country communities. *J Perinatol* 2002; 22(6): 484–495; G. Jones, R. Steketee, R. Black, et al. Bellagio Child Survival Study Group. How many child deaths can we prevent this year? *The Lancet* 2003; 362(9377): 65–71; A. Daar, H. Thorsteinsdottir, D. Martin, A. Smith, et al. Top ten biotechnologies for improving health in developing countries. *Nat Genet* 2002; 32: 229–32; B. Bloom, *op. cit.* note 31.

³⁹ T. von Schoen-Angerer, *op. cit.* note 29.

⁴⁰ A. Daar, *op. cit.* note 36. The use of this example of promising genomics biotechnologies is intended to illustrate the point about useful products that could be developed for low-income settings, rather than to suggest that genomics research, in particular, deserves more support.

currently in use in low-income settings are cumbersome and unsuitable for the context. Molecular diagnostic technologies that are either already in use or are being tested in low-income regions include the polymerase chain reaction (PCR), monoclonal antibodies, and recombinant antigens.⁴¹ Daar et al. report that:

Modifications can make these technologies more suitable for lower-income settings; for example, a PCR-based HIV test that detects the presence of pro-viral DNA in infants has been simplified to use filter paper to process and store blood samples. The DNA can be amplified while the sample is bound to the filter paper, and samples stored this way are heat-stable and can be used for many months. Simple hand-held test devices that rely on the binding specificity of monoclonal antibodies or recombinant antigens to diagnose infection may be easily adaptable to settings without running water, refrigeration or electricity.⁴²

Implementation research

Scientific advances in the study of communicable diseases have enabled prevention, treatment, and in some instances eradication of certain diseases in high-income countries. Despite an increased global investment in diseases that affect low-income countries over the last two decades, there is an alarming gap between investments in innovations in health, such as vaccines, drugs and interventions, and investments in studying how these innovative technologies can best be applied in poorer populations where they could have the largest influence on global health. Implementation research explores how existing interventions can be effectively integrated into health systems and aims to develop strategies for improving access to, and use of, these interventions.⁴³

A 2007 report on childhood mortality research examines research investments by the National Institutes of Health (NIH) and the Bill and Melinda Gates Foundation in developing countries.⁴⁴ The report compared research investments in medical technology (*product research*) with research investments in technology delivery and utilization (*implementation research*). Ninety-seven percent of grants supported product research and 3% implementation research. The authors also estimated mortality reductions

⁴¹ C. Palmer, J. Lindo, W. Klaskala, et al. Evaluation of the OptiMAL test for rapid diagnosis of *Plasmodium vivax* and *Plasmodium falciparum* malaria. *J Clin Microbiol* 1998; 36: 203–206; S. Aidoo, W. Ampofo, J. Brandful, et al. Suitability of a rapid immunochromatographic test for detection of antibodies to human immunodeficiency virus in Ghana, West Africa. *J Clin Microbiol* 2001; 39: 2572–2575.

⁴² A. Daar, *op. cit.* note 36, pp. 230.

⁴³ T. Madon et al., *op. cit.* note 32; N. Barsdorf, *op. cit.* note 27.

⁴⁴ The National Institutes of Health (NIH) and the Bill and Melinda Gates Foundation are the largest public and not-for-profit sources of funds for health research respectively.

from a research funding strategy focused primarily on product research compared with one that also focused on delivery and utilization. The reduction achieved by product research alone (22%) was shown to be one third of what could be achieved if existing technologies were fully utilized. The report points to the serious discrepancy between current investments in research and investments in the research needed to save the lives of the greatest number of children in low-income settings.⁴⁵

Rollback Malaria reports that limited funding has made it difficult for implementation research to keep pace with the development of new interventions for malaria. The effectiveness of existing interventions has been undercut by non-adherence to drug regimens, improper use of long-lasting insecticidal nets and washing walls after indoor residual spraying. Identifying solutions to these and other types of implementation 'bottlenecks' that limit programme effectiveness in lower-income contexts would contribute to the successful implementation of current cost-effective interventions on a broad scale.⁴⁶ The National Institute of Allergy and Infectious Diseases (NIAID) at the National Institutes of Health (NIH) lists implementation research as one of their four priority gaps in malaria research.⁴⁷

Enabling poor populations in diverse contexts to apply solutions that are already available elsewhere should be prioritized in the global research agenda. For the world's worst off, the benefits of these particular types of health research offer a potential for change that has gone largely untapped.

Health systems research

Health systems research focuses on the performance of a country's health services and interventions in the public and private health sectors. It can help identify best practices and prioritize areas that need strengthening. Health system constraints constitute major barriers to achieving acceptable health outcomes in low-income settings. Improvements in health systems can have beneficial effects across multiple diseases by improving service delivery more generally. The systems for delivering existing interventions are seriously deficient and their utilization is inadequate, especially among the poor.⁴⁸ In 2007,

⁴⁵ J. Leroy, J. Habicht, G. Pelto et al. Current priorities in health research funding and lack of impact on the number of child deaths per year. *Am J Public Health* 2007; 97: 219–223.

⁴⁶ Roll Back Malaria, *op. cit.* note 30.

⁴⁷ NIAID. 2008. NIAID Research Agenda for Malaria. Bethesda, MD: NIAID. Available at: <http://www.niaid.nih.gov/topics/Malaria/Documents/researchagenda.pdf> [Accessed 19 Aug 2010].

⁴⁸ J. Bryce, S. el Arifeen, G. Pariyo, et al. Reducing child mortality: can public health deliver? *The Lancet* 2003; 362: 159–164; C. Victora, A. Wagstaff, J. Schellenberg, et al. Applying an equity lens to child health and mortality: more of the same is not enough. *The Lancet* 2003; 362: 233–241.

Dr. Margaret Chan, Director-General of the World Health Organization, succinctly captured the gap in her Beijing speech:

Something is wrong. For the first time, public health has commitment, resources, and powerful interventions. What is missing is this: the power of these interventions is not matched by the power of health systems to deliver them to those in greatest need, on an adequate scale, in time. Research on health systems has been so badly neglected and underfunded.⁴⁹

While health systems research has been identified as critical to scaling-up interventions, few research priority setting exercises have properly addressed health systems research. This may be one reason why funding for the field has been relatively limited.⁵⁰ In 2004, the ministerial summit in Mexico (convened to discuss key challenges in international health research) drew attention to the historic neglect of health systems research and called for increased health systems research funding globally and investment in national institutional capacity for health systems research. While the last decade has seen an increased interest in, and support for, health systems research, small grants and lack of coordination between funders have inhibited sustained capacity development over time.⁵¹

There are still many unanswered questions about how to strengthen health systems and more resources are needed both to answer these questions and to build health systems capacity within low-income settings.⁵² Current assessments of the global health research investment landscape point to the need for better identification

⁴⁹ S. Hoffman, J. Røttingen, S. Bennett, et al. 2012. Background Paper on Conceptual Issues Related to Health Systems Research to Inform a WHO Global Strategy on Health Systems Research: A Working Paper in Progress. Available at: <http://www.who.int/alliance-hpsr/alliancehpsr-backgroundpaperhsrstrat1.pdf> [Accessed 19 Mar 2016].

⁵⁰ M. Ranson & S. Bennett. Priority setting and health policy and systems research. *Health Research Policy and Systems* 2009; 7: 27. Available at: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2796654/pdf/1478-4505-7-27.pdf> [Accessed 19 Mar 2016].

⁵¹ S. Bennett, T. Adam, C. Zarowsky, et al. From Mexico to Mali: progress in health policy and systems research. *The Lancet* 2008; 372: 1571–8. Available at: http://www.who.int/alliance-hpsr/resources/alliancehpsr_peersara2008lancetmexico.pdf [Accessed 19 Mar 2016]; S. Bennett, L. Paina, C. Kim, et al. 2010. What must be done to enhance capacity for Health Systems Research? Background paper for the global symposium on health systems research. Montreux, Switzerland: World Health Organisation. Available at: http://www.healthsystemsresearch.org/hsr2010/images/stories/4enhance_capacity.pdf [Accessed 19 Mar 2016].

⁵² World Health Organisation (WHO) Taskforce on Health Systems Research. 2005. The Millennium Development Goals will not be attained without new research addressing health system constraints to delivering effective interventions. Geneva, Switzerland: WHO. Available at: http://www.who.int/rpc/summit/en/Task_Force_on_Health_Systems_Research.pdf [Accessed 19 Mar 2016].

of global research priorities for health systems research.⁵³ The 2013 World Health Report calls for increased international and national investment in research aimed specifically at improving coverage of health services within and between countries. The report also highlights the importance of closer collaboration between researchers, policymakers, and the public health programmes that are close to the supply of and demand for health services.⁵⁴

6. OBJECTIONS

Focusing on the worst off is sometimes inefficient

We have argued that the social value of research is normally highest when the research is aimed at improving the situation of the globally worst off. However, there are cases in which the cost of benefiting the worst off is likely to be astronomically high relative to the expected benefits that they will receive. For example, children with Tay-Sachs disease normally die by age 4 after severe mental and physical deterioration. These children are surely among the global worst off, according to our criteria. But, it might be argued, the prospects for a cure for Tay-Sachs are very small and the number of children affected relatively few. Prioritizing such research might be thought to be an inefficient use of resources.

In response, note that moderate prioritarian views, like the one we endorse, consider both degree of disadvantage and the amount of benefit to be relevant in judging the value of an option. If the expected benefit of Tay-Sachs cure research were very low – and this is an empirical question on which we do not have a view – then that would be a reason not to give it highest priority, even though it would be aiming to help people who are among the very worst off. Research with a higher chance of benefiting more people who are slightly less disadvantaged might be judged to have higher social value and so be preferable.

This objection helps reveal the extent to which our contention – that the most socially valuable research will focus on the health problems of the worst off – depends on the facts. Because children who die young are so

badly off and because we know that many young deaths in LMICs could be prevented, there is good reason to think that research that focuses on these populations will generally produce large benefits for the worst off. As the Tay-Sachs example suggests, this may not universally be the case.

Focusing on the worst off is sometimes not relevant

A related concern might arise with regard to the scope of application of our account of social value. For various decision-makers, focusing on the global worst off is not relevant to the choices they face. For example, a funding agency might have a mandate to support cancer research based on domestic needs, a researcher might not be working in a disease area that is especially important to the globally worst off, and RECs do not get to decide what types of research they review. This article has focused on scenarios in which decision-makers are in a position to choose research for the global worst off; what can we say to these other actors?

Note, first, that our account of social value is quite general. Any proposed research project could, in principle, be assessed for both the expected benefits that it will generate and for the degree of disadvantage of the expected beneficiaries.⁵⁵ Second, however, making this assessment requires not just an account of what social value consists in but also a lot of information about the options that are being chosen among. Assessing the expected benefits of a research project requires understanding the current state of knowledge about the topic being researched, the prospects for the study to advance that knowledge, and what can be done for patients and others on the basis of the possible results of the project. (These are, of course, challenges for assessing the social value of a project on *any* conception of social value.) Assessing the degree of disadvantage of the beneficiaries requires data on, among other things, disease burden, life expectancy, various dimensions of poverty, and so forth.⁵⁶ This is all information that is highly context-specific, will vary from project to project, and is best analysed by experts in the research area in question.

Bearing these caveats in mind, we would suggest that the cancer research agency could guide its choices of what research to support by assessing not just the disease burden of different cancers and the knowledge gaps that

⁵³ M. Ranson & S. Bennett. Priority setting and health policy and systems research. *Health Research Policy and Systems* 2009; 7: 27. Available at: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2796654/pdf/1478-4505-7-27.pdf> [Accessed 19 Mar 2016]; S. Bennett et al., *op. cit.* note 49; B. Pratt & B. Loff. Health research systems: promoting health equity or economic competitiveness? *Bull World Health Organ* 2012; 90: 55–62. Available at: <http://www.who.int/bulletin/volumes/90/1/11-092007/en/#> [Accessed 19 Mar 2016].

⁵⁴ World Health Organisation (WHO). 2013. The World Health Report 2013: Research for universal health coverage. Geneva, Switzerland: WHO. Available at: <http://www.theglobalfund.org/en/archive/annual-reports/> [Accessed 19 Mar 2016].

⁵⁵ Our account is also general in that it can be applied by people who differ with regard to the benefits that they think should count when assessing social value or who disagree with us about the correct conception of disadvantage: they can still assess social value as a function of expected benefit and the degree of disadvantage of the beneficiaries, using their preferred currency for benefits and their preferred conception of disadvantage.

⁵⁶ D. Sharp & J. Millum. *op. cit.* note 15.

exist, but also how early in life these cancers are killing people and whether they differentially affect different sub-populations. High rates of cervical cancer in women of low socio-economic status should, all else being equal, get higher priority than similar rates of prostate cancer in older, wealthier men. A researcher with expertise in heart disease might choose to develop a research programme that focuses on the prevention of heart disease in South Asia or Sub-Saharan Africa, rather than Europe. She might apply to many of the same sources of funding, but the studies she would propose would be different. An REC assessing an influenza challenge study might be more willing to allow participants to take on heavy burdens or higher risks, if the outcome of the study is expected to have particular benefits to patients with comorbidities or weakened immune systems, i.e. to patients who were worse off than the average person at risk for seasonal influenza. Although these other scenarios have not constituted the primary focus of this article, our account can be helpful for more than just promoting research on the global worst off.

Will research actually help the worst off?

Research versus care

Finally, it might be objected that the focus on research is itself misguided. Given what we know already about which interventions would save the lives of children in LMICs, shouldn't we be supporting programmes that deliver those interventions, rather than engaging in more research with benefits a long way down the road?

We do think that there are still important research gaps, as the examples given throughout the article illustrate. In fact, the knowledge gaps are particularly pressing when it comes to getting proven, effective interventions to the people who need them most. However, it might well be true that the absolute best use of social resources would be in funding the delivery of known interventions. For that matter, it might turn out that the best way to help the worst off would not involve traditional health interventions at all, but investment into sanitation, education, the empowerment of women, and so forth.

The question of the best way to help the people in the world who are most disadvantaged is very important. For people and institutions that have complete discretion over how they use their funds, it is an open question whether they should be supporting health research to help the worst off or spending their money in other ways. However, most of the people and institutions that have to make decisions about health research do not have such discretion. Research funding bodies, for the most part, do not have the option of ceasing to fund research and doing something else entirely. For example, the mission statement of the NIH says: 'NIH's mission is

to seek fundamental knowledge about the nature and behaviour of living systems and the application of that knowledge to enhance health, lengthen life, and reduce illness and disability.' People working for NIH must make their decisions within the constraints of this and other legislated goals. Likewise, RECs do not make decisions about what they will review; they will review the ethical appropriateness of proposed research studies. Within that constraint, it is helpful for REC members to have a conception of social value to apply to the studies they review. It is to those who are making decisions about health research specifically that our arguments in this article are addressed.

7. CONCLUSION

This article proposes that the social value of health research should be conceptualized as a function of both the expected benefits of the research project and the priority that the beneficiaries deserve. People deserve greater priority the worse off they are. Insofar as it is possible to compare the expected benefits of different research studies, research that is likely to generate greater improvements in the welfare of the worst off is of higher social value and should be preferred to research that is less socially valuable.

This conception of social value can be applied for at least two important purposes. (1) In evaluating the ethics of proposed research projects, such as when RECs review research protocols. Among other conditions, the social value of a project must be sufficient to justify the risks and burdens of the research for research participants and others who may be affected. Both the amount of benefit and the degree of disadvantage of the beneficiaries is relevant to this judgment. (2) In health research priority setting when research funders, policy makers, and researchers decide between alternative research projects. All else being equal, it is better to fund and conduct research with higher social value. Insofar as it is possible to compare the expected benefits of different research studies, research that is likely to generate greater improvements in the welfare of the worst off is of higher social value and should be preferred to research that is less socially valuable.

Assessments of the social value of research should include looking at both the diseases that the research targets and the type of research. Just as certain diseases impose a greater burden on people who are more disadvantaged, so certain types of research are more likely to benefit people who are more disadvantaged. The types of research that offer greater social value because they are likely to benefit the worst off include research on products appropriate for low-income settings, and implementation and health systems research towards effectively

implementing existing interventions in resource-poor health systems. Since international donors fund the majority of global health research, meeting this social value requirement relies as much on the international research community as it does on national policy makers.

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