

Correspondence

Research Ethics Committees in Africa: Building Capacity

Solomon Benatar

In response to the case study by Kass et al. on research ethics committees (RECs) in Africa [1], the following additional information is provided about capacity building for research ethics in South Africa.

South Africa has two programs funded by the Fogarty International Center: the International Research Ethics Network for Southern Africa (IRENSA; see <http://www.irensa.org>) based in Cape Town and the South African Research Ethics Training Initiative (SARETI; see <http://shsph.up.ac.za/sareti/sareti.htm>) that allies the Universities of Pretoria and KwaZulu-Natal. Each of these programs has a different focus and both are making highly valued contributions to capacity building in international research ethics in Southern Africa.

The goal of the IRENSA diploma program is to develop and nourish sustainable multidisciplinary expertise in international research ethics and bioethics in southern Africa. It prepares mid-career health and allied professionals from South Africa and other developing nations in Africa to assume positions of leadership in research ethics in their home institutions. This program is unique on the African continent in focusing exclusively on training mid-career professionals (who cannot take the time or leave to undertake full-time graduate work), in three intensive two-week modules spread throughout one year, with assignments carried out at their home institutions.

In four years IRENSA trained 49 mid-career professionals (17 men, 32 women, 20 white, 29 black) drawn from 20 institutions in South Africa and from 11 institutions in eight other low-income African countries. Sixteen students serve as chairs, deputy chairs, or secretaries of RECs. Students reflect professional training in many disciplines, including science, medicine, nursing, social sciences, law, and pharmacology. Eighteen students hold doctoral degrees and represent a broad spectrum of health organizations. In addition, our annual two-day seminars in research ethics have reached over 40 attendees.

SARETI's goal is to build capacity for ethical review of health research and strengthen Africa's institutional training capacity necessary to achieve and sustain this aim. It offers a multidisciplinary, modular master's degree program with funding for nine trainees over four years, an advanced, non-degree program resulting in a certificate with funding for 16 trainees, and a training program for 40 ethics review committee members. In 2003 SARETI co-hosted, with the HIV/AIDS Vaccines Ethics Group, a two-day training workshop for over 40 members of South African RECs, and in 2004 it offered a three-week Ethics Review Committee Training Program sponsorship to nine South African applicants.

A spin-off of these educational programs has been the formation of a network of Chairs of South African Human Health Research Ethics Committees. This has significantly improved liaison across the country, reduced the potential for shopping around by researchers, and has enhanced the stringency with which protocols are reviewed. A newsletter from Stellenbosch University on research ethics activities in

the country draws attention to current debates and events and facilitates networking [2]. The recent stand taken by the chairpersons of RECS in South Africa not to permit studies that do not provide insurance cover for research-related injuries is one example of how improved knowledge and coordination in South African RECs are making such a contribution [3]. ■

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Research Ethics Committees in Africa: Authors' Reply

We thank Dr. Benatar [1] for pointing out that South Africa has two Fogarty-funded bioethics training programs: one that focuses primarily on providing short-term training to mid-career professionals from Southern Africa; and another that provides modular training in research ethics to professionals from the African continent. In addition, there are now several other Fogarty-funded training programs that either target African professionals exclusively or include African professionals, among others, in their programs (see http://www.fic.nih.gov/programs/training_grants/bioethics/index.htm). All of these programs share the goal of increasing professional capacity in bioethics and research ethics on the African continent.

Our own paper demonstrated that training even a small number of individuals can make a difference in changing policy and practice regarding research ethics in several institutions; that so many training efforts are now ongoing is a major step forward. Again, having more people teaching and discussing research ethics and starting and staffing research ethics committees will never itself guarantee that research with humans is more ethical, but it seems to be a critical first step. Capacity development for Africa still remains a challenge and worthy of increasing investments in global health. ■

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World Social Health Insurance: Strengthening Health Systems in Low-Income Countries

Wim Van Damme

The paper by Ooms et al. [1] is very timely and stimulating. It launches the debate on how to finance globally the right to health care in low-income countries. This is a most welcome step, going beyond the usual aspirational rhetoric. I would like to contribute to the development of this idea.

First: the name. I fear that "World Health Insurance" may create confusion. Health insurance can be a pure risk-sharing mechanism without built-in solidarity between rich and poor, healthy and less healthy, or between old and

young. But the concept of social health insurance—as the statutory health insurance systems in much of continental Europe are usually referred to—is intrinsically based on such solidarity, which certainly is one of the values underpinning Ooms' proposal. I therefore propose the name "World Social Health Insurance."

Second: the contribution by low-income countries. Ooms et al. propose 15% of government budget as a fair contribution, the so-called Abuja target. I fear, however, that this target does not create the right incentive for governments in low-income countries, many of whom are reluctant or unable to tax their citizens, even the richer ones, and fail to create a decent tax basis. Consequently, some governments have extremely lean budgets, even below 20% of gross domestic product (GDP) [2], while the World Bank estimates that at least some 30% of GDP is needed to sustain a well-functioning state. I therefore think that calculating the contribution of low-income countries to their countries' health system as 4% or 5% of GDP would constitute a fairer burden sharing mechanism.

Third: the contribution of high-income countries. Ooms et al. propose that rich countries adopt a burden sharing similar to their contribution to World Bank's IDA 14 (the 14th replenishment of the International Development Association). This normalizes the low commitment of donors such as the United States, contributing in absolute terms hardly more than the United Kingdom or Japan, while its total GDP is much larger. I therefore think that for high-income countries, a contribution linked to total GDP would be fairer: e.g., 0.15%, which would be a bit more than one-fifth of the 0.7% target that most OECD countries have committed to as total overseas development assistance. Alternatively, and more in line with the concept of social health insurance, high-income countries could dedicate a share of domestic health expenditure (e.g., 1%) to world social health insurance. With total health expenditure in the United States now reaching US\$2,000 billion [3], this modest 1% would already come close to the total needs as estimated by Ooms.

Lastly: operationalization. How to operationalize the massive scale-up of services proposed, given present human resource constraints and institutional capacities, is still a huge challenge. Whether it is best to take inspiration from the experience with rounds of competitive proposals, followed by performance-related disbursement, as the Global Fund uses, or whether the proposal of the Global Alliance for Vaccines and Immunisation (GAVI) to link disbursement to strategic government plans and sector-wide approaches would be more successful, remains to be explored.

We sincerely hope that the idea launched by Ooms et al. catches on, so that health services in low-income countries can rapidly expand. This can be seen, as Garrett convincingly argues [4], as an expression of a moral duty, as a form of public diplomacy, or as an investment in self-protection. Whatever the drive, there are enough reasons to start preparing it backed by long-term reliable funding, fairly shared between all stakeholders, according to their purchasing power. ■

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Circumcision for HIV Prevention: Failure to Fully Account for Behavioral Risk Compensation

Seth Kalichman, Lisa Eaton, Steven Pinkerton

Three randomized controlled trials (RCTs) of male circumcision (MC) have been halted when interim analyses showed significant reductions in HIV infection among men who received this intervention [1–3]. Modeling suggests that increased MC coverage in southern Africa could prevent as many as 2 million HIV infections over ten years [4]. Moreover, the cost-effectiveness analysis by Kahn et al. recently published in *PLoS Medicine* indicates that MC could be cost-saving [5]. However, the protection of MC may be partially offset by increased HIV risk behavior, or “risk compensation,” especially reduction in condom use or increases in numbers of sex partners. Risk compensation occurs when individuals adjust their behavior in response to perceived changes in their vulnerability to a disease [6]. Risk compensation may be especially important for MC because avoiding the sexual dissatisfactions of condom use and the desire to have more sex partners are likely to be significant motivations for men to seek circumcision [7]. In South Africa, 73% of men between the ages of 15 and 24 report using condoms during the last time they had sex [8]. It is difficult to imagine a convincing public health message that effectively influences men to undergo circumcision and continue to consistently use condoms.

Circumcised men in the ANRS 1265 trial reported 18% more sexual contacts at follow-up than did uncircumcised men, but no other sexual behavior differences were obtained [1]. However, for ethical reasons all men in MC RCTs receive ongoing risk-reduction counseling and free condoms, which reduces the utility of these trials for estimating the potential behavioral impact of MC when implemented in a natural setting. One model of the potential impact of MC did not take into account risk compensation [4], but noted that “increases in risk-taking behaviour among circumcised men could reduce the benefit of MC.” Based on the 18% difference in sexual contacts for circumcised and uncircumcised men in the ANRS 1265 trial and the assumption that “risk compensation might be higher in a

nonresearch program scale-up.” Kahn et al. [5] adjusted the 60% effectiveness estimate obtained in this RCT downward to 50% to reflect a 25% increase in sexual risk behaviors among circumcised men. Although Kahn et al.’s model explicitly incorporated the increased risk of HIV acquisition associated with risk compensation, it did not consider the impact of risk compensation on the HIV transmission risk of HIV-infected circumcised men, or on circumcised men’s risk for non-HIV sexually transmitted infections (STIs).

There is no evidence that circumcision increases or decreases the risk of HIV transmission by HIV-infected men. However, risk compensation by HIV-infected circumcised men will substantially increase the risk of transmission to their sex partners. This suggests that, in the short term at least, circumcision would reduce the incidence of HIV among men, but increase the incidence among women, translating to increased prevalence among women, which in turn translates to greater risk to men. Epidemiological models of MC should take this dynamic into account.

Countless studies have shown that ulcerative and non-ulcerative STIs account for at least some of the rapid increases in HIV transmission in southern Africa [9]. Non-HIV STIs are associated with a 2- to 5-fold increase in HIV transmission risk in countries with low and high rates of MC [9]. In areas with prevalent STIs, the relative increase in men’s STI-associated HIV risk can be as high as 60% to 340% [10]. Circumcision likely reduces the risk of acquiring a non-HIV STI and may be partially responsible for the decreased HIV risk observed in circumcision RCTs [1]. Nevertheless, the failure of models to account for increased STI risk due to risk compensation likely inflates estimates of averted HIV infections. Estimates of HIV risks resulting from increased exposure to STIs that coincide with reductions in condom use have been included in previous models of the cost-effectiveness of HIV prevention interventions [11] and should be included in MC models. ■

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Circumcision for HIV Prevention: Authors' Reply

The issues regarding risk compensation raised by Kalichman et al. [1] are cogent for refining modeled estimates of the impact of male circumcision (MC). Even more important is to empirically monitor risk compensation during the scale-up of male circumcision.

As Kalichman et al. note, we included in our modeling of MC impact a risk compensation level for men susceptible to HIV above that observed in the Orange Farm trial.

However, we did not incorporate risk compensation among the HIV infected, an adjustment which would have lessened the estimated benefits of male circumcision. These two biases are offsetting. Another conservative bias in our analysis is that we used the per-randomization protective effect of 0.60, rather than the per-clinical protocol protective effect of 0.70. Arguably, effectiveness in practice is better captured by the latter, and this would increase the estimated benefits of male circumcision.

The inclusion of the effects of non-HIV sexually transmitted infections (STIs) as risk co-factors would add a useful dimension to our analysis. The net effect could be to decrease or increase MC impact. As Kalichman et al. note, increased STIs associated with risk compensation in newly circumcised HIV-infected men would likely lessen MC impact. However, in a concentrated epidemic setting where STIs play a greater role in HIV transmission than in South Africa, the STI-reducing effects of MC in HIV-susceptible men could further increase the benefits of MC in preventing HIV.

Regarding the magnitude of risk compensation, we are encouraged by recent data suggesting that MC does not increase risky behavior, and may lead to a transient decrease [2]. However, we, like Kalichman et al. and others, are eager to see the favorable experience in clinical trials carried over to routine and widely operating programs. Thus, the current efforts to plan MC scale-up emphasize the need for an MC procedure that incorporates effective risk reduction counseling. In the context of a medicalized adult male circumcision model, and a clear public health message, risk compensation can be minimized. Thus, a great value of MC scale-up is the opportunity to directly deliver a strong behavioral prevention message. A similar risk reduction message has worked well with antiretroviral therapy in Africa [3].

The ultimate and critical test is monitoring risk behaviors in communities where MC is scaled up. If risk compensation is higher than expected, redoubled risk reduction methods will be imperative. ■

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Counterfeit Artemisinin Derivatives and Africa: Update from Authors

Paul N. Newton, Michael D. Green, Facundo Fernandez

Since the publication of our article on counterfeit artesunate in June 2006 [1], further information has become available which we would like to report, as it has public health significance. An additional two counterfeit artesunate “types” with distinguishing features of the packaging have been found in mainland Southeast Asia, bringing the number of physical types to at least 14. For details see “Fake Artesunate Warning Sheet Number 5a” [2], an update (dated August 2006) to that published as supplementary material to the above paper.

In addition, we would like to bring readers' attention to the newspaper reports of counterfeit artesunate and dihydroartemisinin seized from ladies' handbags at Lagos airport [3].

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Children Born to HIV-Infected Mothers in Côte d'Ivoire: Methodological Clarifications Needed

Moussa Sarr

In their recently published paper, Becquet et al. [1] found that the 2-years rates of adverse health outcomes were similar among short-term breast-fed and formula-fed children. Mortality rates also did not differ significantly between these two groups and, after adjustment for pediatric HIV status, were similar to those observed among long-term breast-fed children. These results confirm the findings of two previous trials in Kenya [2] and in Botswana [3], highlighting the fact that with adequate support, alternatives to prolonged breast-feeding can be safe options for mothers to prevent mother-to-child transmission of HIV in African settings. HIV-infected mothers who opt for alternatives to breast-feeding to protect their children from HIV infection should be provided the necessary support to make their choice feasible.

There are, however, some methodological clarifications that need to be made regarding the incidence rates of diarrhea, acute respiratory infection, and malnutrition. It was not clear if all repeated episodes of diarrhea and acute respiratory infection were taken into account to compute the incidence rates. A number of epidemiologists have also been advocating the use of longitudinal prevalence instead of incidence for the longitudinal measure of morbidity associated with childhood diarrhea [4]. The longitudinal prevalence is defined by the number of days of diarrhea divided by the total number of days of observation for each child. Longitudinal prevalence was found to be a better predictor of long-term health outcome in relationship to childhood diarrhea [4]. ■

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Placental Malaria: Hypertension, VEGF, and Prolactin

Roy Douglas Pearson

The findings by Muehlenbachs et al. [1] that placental malaria (PM) is associated with hypertension in first-time mothers aged 18–20 years is significant, and not to be explained at this time of writing. The authors also provide data suggesting that the maternal–fetal conflict, during chronic PM and hypertension in first-time mothers, involves the VEGF pathway.

Previously [2–5], I have posited that prolactin might have a role in PM and these new findings might provide further indirect evidence for such a role. It should be remembered that there is an extensive and decades-old literature (see Horrobin's chapter 23 in [6]) on the role of prolactin in hypertension; and more specifically, the relationship between prolactin and pregnancy-related hypertension [7,8].

Regarding the VEGF pathway, Malaguarnera et al. [9] have recently shown that prolactin induces VEGF production in human macrophages. It is conceivable that hyperprolactinemia (pituitary and/or placental) could up-regulate placental macrophage production of VEGF.

Space does not permit a discussion of the well known fact of increased pregnancy-related prolactin in first-time mothers, but this has been noted elsewhere [2] concerning maternal malaria.

Although there has been controversy of late [2,10], regarding my “prolactin hypothesis” in maternal malaria, it is time definitive experiments be conducted to ascertain if prolactin is playing a role in PM, and in other infectious diseases as well. ■

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Pollution and Tuberculosis: Outdoor Sources

Aaron Cohen, Sumi Mehta

The meta-analysis by Lin and colleagues [1] is important for two reasons. It evaluates the evidence concerning exposure to combustion-derived air pollution and tuberculosis (TB), and it quantifies the risk of TB associated with three important sources of exposure: tobacco smoking, environmental tobacco smoke, and indoor burning of solid fuels. Their analysis invites speculation about the possible role of another combustion source: outdoor urban air pollution, a growing problem in developing countries where the burden of disease from TB is greatest.

Combustion-source air pollution affects resistance to infection via effects on airway resistance, epithelial permeability, and macrophage function [2]. Studies suggest a specific role for fine particles less than 2.5 micrometers in diameter (PM_{2.5}) [3]. PM-associated transition metals, e.g., iron, are thought to produce oxidative stress in the lung, hypothesized to be a common factor in a range of adverse effects [4], and have been associated with altered host defenses in rats [5]. As Lin notes, the amount of iron in the lung has also been hypothesized to adversely affect the progression of TB [6,7].

Air pollution from outdoor sources, such as motor vehicles, industry, and neighborhood-level solid waste burning, is associated with increased morbidity and mortality from respiratory infections in children and adults [8,9]. Only one study of outdoor air pollution and tuberculosis has been reported in the peer-reviewed literature to date [10], but one might speculate that outdoor air pollution would have a similar impact on TB infection and/or progression of disease via the mechanisms described above.

People in urban areas of developing countries are exposed to the highest levels of outdoor air pollution in the world, which each year impose an estimated burden of hundreds of thousands of deaths and millions of years of healthy life lost from cardiovascular disease, selected respiratory diseases, and lung cancer [11]. TB was not

considered due to lack of evidence, so these estimates assume that outdoor air pollution plays no role. If, however, air pollution exposure increases the risk of infection, illness, or death from TB, then the attributable burden of disease would be even greater.

Environmental policy in developing countries should be informed by the best and most complete information on the health effects of air pollution. New research efforts should address health outcomes of regional relevance, such as TB and childhood respiratory illness. Since TB is endemic in many developing countries, even a small increase in risk could translate into a large attributable burden. Research on outdoor air pollution and TB seems warranted. ■

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Training and Experience of Peer Reviewers: An Additional Variable to Consider

Erik Kulstad

I read with interest your article [1] on peer reviewers' review quality and the relationship to previous training and experience, particularly the fact that your study found no easily identifiable types of formal training or experience that predict reviewer performance. As you conclude, without a

better understanding of the skills in scientific peer review, journals and editors will have difficulty in systematically improving their selection of reviewers.

I wonder if an additional variable not examined in your study may prove potentially predictive of performance, namely the time committed by a reviewer to the review process in general, or a given review in particular. This data point could easily be provided by a reviewer, albeit with the caution that a self-reported number will have some subjectivity that is immeasurable. This variable could be specified either as the a priori time that an individual reviewer is willing and/or able to put towards completing a review or a self-reported time spent in actually completing a review. Either a simple dichotomized variable, say, less than four hours or greater than four hours spent on a review, or a measurement on a continuous scale, might be revealing.

Perhaps if the self-reported time commitment to a given manuscript review is found to correlate with quality of the review in a univariable or multivariable model, an additional criteria for selecting reviewers can be based on this question. A positive correlation might also explain the paradoxical findings of worse performance when being a peer reviewer for another journal or when serving on an institutional review board. Increased availability of time to commit to the process may also explain the findings of improved review quality with younger training status, if one presumes that free time diminishes with age! ■

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Training and Experience of Peer Reviewers: Is Being a “Good Reviewer” a Persistent Quality?

Ignacio García-Doval

After reading your interesting paper [1], I think that all editors will feel a bit disappointed that there are no magic answers to their practical question: who will be a good reviewer for this paper?

So, they will probably stick to the old practice: try to get a good group of reviewers and ask them to do it. However, this way of working is based on the assumption that being a good reviewer is a long-lasting quality, so that doing a good review predicts that the next review will also be good.

I could not find a clear answer to that question in this paper. I think that with their dataset the authors can probably provide us with an answer that will reassure editors on their

decision to stick to the group of reviewers that have produced good reviews in the past.

Would they be so kind? ■

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Training and Experience of Peer Reviewers: Authors’ Reply

Dr. Ignacio García-Doval [1] raises an interesting question—if a reviewer initially proves themselves of high quality at a particular journal, can we count on them to continue in this vein?

We have not examined this as thoroughly as the predictive factors, but we have found that good reviewers, on average, continue to produce good reviews for many years. However, their performance is not so consistent that one can completely cease monitoring them, because a modest proportion will deteriorate, presumably due to changes in their personal or professional lives. We have had reviewers who were reliably good for many years, but whose scores then steadily deteriorated until we were forced to retire them.

This reinforces our recommendation that all but the most resource-poor journals should routinely rate reviewers, something not hard to do in this era of ubiquitous computer databases. We recommend a look at those ratings about once a year, and feedback of some kind to those doing poorly. Another benefit is that this also identifies the high performers, who can then be rewarded in some way for their donated labor (a note of thanks, inexpensive objects with your journal logo, free continuing medical education for their review time, etc.). Consistent very high performers also serve as a good source for future editorial board appointments. ■

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