

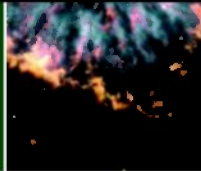
For young readers

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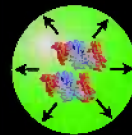
How stars produce elements

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Life science prize essay

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LETTERS

edited by Etta Kavanagh

Deciding Who Should Get the Flu Vaccine

THE POLICY FORUM “WHO SHOULD GET INFLUENZA VACCINE WHEN NOT ALL CAN?” by E. J. Emanuel and A. Wertheimer (12 May, p. 854) has initiated a welcome debate on ethical considerations during a pandemic. However, the authors’ proposed guiding principle for allocating vaccine in a situation of scarcity—the “investment refinement of life-cycle principle including public order” or IRPOP—gives rise to some serious problems.

Emanuel and Wertheimer weigh the investments a person has made in her life balanced by the amount left to live, i.e., the amount of unfulfilled potential. The authors conclude that this would favor people aged 13 to 40 years old. However, in most societies, there is a great difference in both life prospects and life expectancy in different social groups (1). For instance, a white 16-year-old teenage boy in the United States has on average a 77% chance of reaching age 65, while an African-American teenager from Harlem, New York, has only a 37% chance (2). Taking the IRPOP principle seriously, we should not give the “socially challenged” black youngster a high priority for vaccination. This would, of course, perpetuate existing injustices. We can always claim that all 16-year-olds ought to have the same life expectancy and vaccinate them equally, but then we have disregarded the investment principle and are back to the unrefined but egalitarian life-cycle principle.

No man is an island. To invest, you usually expect returns, and to realize your own interests, hopes, and plans, you usually have to realize someone else’s too. Even though this was not an aim of the

IRPOP principle, the effect of favoring those with the potential to realize their interests, hopes, and plans would be to favor those who are most profitable. We are then giving provisions for activities that uphold vaccine production, health care, or public order and economic profitability in general. That the chronically unemployed should get a lower priority for vaccination than those who have a job would in most societies be quite unacceptable. We have to find other and more equitable grounds for prioritizing than realizable life investments.

What are the characteristics of people between adolescence and middle age, besides having unfulfilled lives and being most productive? They are also those taking the highest risks in life (probably just because they have these unfulfilled hopes). Perhaps some of them are also willing to take the risk of acquiring influenza to let someone else get vaccinated first. Not only self-interest but also willingness to sacrifice your own interests for others give weight to ethical considerations. To endorse a principle that prioritizes individual resources and not some aspect of the common good would probably offend many, were they asked. So that is precisely what we should do. Go and ask.

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Response

ONE AIM OF THE INVESTMENT MODIFICATION of the life-cycle principle was to present a clear alternative to two principles for the allocation of influenza vaccine in a pandemic: (i) save the most lives, which would give higher priority to the elderly, and (ii) a pure life-cycle principle (or save the most life years), which would give higher priority to the youngest infants. We were aiming to advance a principle that is committed to the equal worth of all persons and yet recognizes morally relevant distinctions among them.

Holmberg charges that we would favor the “most profitable.” We did not articulate every ethical principle relevant to this issue, mainly

because we assumed that they would operate within a more general framework that includes such principles as no racial and no sexual discrimination. Hence, the investment modification principle gives higher priority to a white adolescent than a white infant; we reject giving higher priority to a white adolescent than a black adolescent or a girl over a boy.

Although society might benefit more from saving the more productive than the less productive, that is not the sort of “investment” that is embedded in the investment modification of the life-cycle principle. The investment in youths is from childrearing, education, love, and attention, and their own efforts at self-development; the “return on investment”

is more in the way these people at age 20 or so can then develop and realize their life plans. This is something that can be, if not fully realized, then progressively realized after age 20 or so. Much will be fulfilled before 65. This gives a reason to give priority to all adolescents, not only those who have a higher likelihood of living until 65. We thought we made this clear when we rejected the World Health Organization’s disability-adjusted life years (DALYs) with its prioritization based on those who are “contributing to the well-being of others” through earning power or caregiving.

Finally, we do not understand how Holmberg would want to give weight to the “common good” as opposed to individuals. If some-



one wants to forego receiving a vaccine for the sake of the common good, he can always do so.

Doubtless, any principle of rationing will offend many. We think it unlikely that this is an issue that can be fruitfully resolved by a referendum or public opinion poll, and so although we would welcome a lively debate, we think that policy-makers must assume the responsibility of producing the principles that are most ethically defensible.

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The Cost of Access to HIV Treatment

OUR RESEARCH (1) CATALOGED ALL RANDOMIZED, controlled trials of interventions for HIV/AIDS that were conducted in Africa from 1987 to 2003. We identified 77 trials overall; of these, only 10 were testing approaches to HIV/AIDS prevention. After reading the exchange "HIV research and access to treatment" by M. Warren and "Response" by R. M. Grant *et al.* (Letters, 13 Jan., p. 175), we attempted to quantify the number of seroconversions occurring in the 53,144 participants included in all 10 trials. Trials were conducted in seven countries and differ in terms of length of follow-up, participant risk profile, and seroconversion rate, presenting a challenge to economic modeling. At an estimated overall annual seroconversion rate of 2.5% and using the numbers from these trials, we estimate that 1329 people would contract the virus each year.

Because cost-effectiveness data are limited, we used data from a recent South African study (2) measuring the cost of antiretroviral (ARV) provision (including monitoring, related care, and hospital inpatient days, but excluding indirect costs) to estimate the costs of treating 1329 seroconverted participants. At current South African public-sector costs of \$1342 per person per year, annual provision of antiretroviral treatment to all participants would cost \$1,783,518. At anticipated public-sector prices for locally manufactured drugs, per-person per-year costs would drop to \$793, reducing the overall costs for all those seroconverting to \$1,053,897. These annual costs are modest and would remain so even if doubled or tripled to account for longer durations of follow-up and for potentially higher costs for small numbers of treatment cohorts or for areas whose treatment costs may exceed those of South Africa.

Costing out the expenses associated with providing ARV treatment to those who seroconvert reveals the weakness of arguments suggested by Grant *et al.*, that offers of "a lifelong guarantee of treatment could exhaust limited research resources and does nothing for those who elect not to participate in research." If ARV treatment costs are as modest as we project (and we strongly recommend that formal cost analyses be done), sponsors of clinical HIV research can surely afford to provide the additional resources necessary to ensure ARV treatment to those who seroconvert during trials. Providing this benefit will also protect those who do not participate in research, because persons receiving supportive ARV treatment and associated care will be less likely to transmit their infection to others in their communities.

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3. The authors are grateful to Ruanne Barnabas and Timothy Law Snyder for their comments on an earlier version of this letter.

Response

WE ADVOCATE STRENGTHENING TREATMENT programs for all people, including those who seroconvert during prevention trials. The Global Fund, PEPFAR, and other treatment programs currently receive substantial funding from sponsors who also support prevention research. Long-term HIV care for people who become infected during HIV prevention trials is not the moral obligation of researchers (1), any more than long-term treatment of cardiovascular events is the moral obligation of investigators in primary prevention trials of cardiovascular disease.

HIV infection has not been an adverse event of prevention study participation. Rather, HIV infection arises from behaviors

and circumstances that continue despite provision of the best prevention services, which are provided to all study participants. Importantly, reported risk behavior routinely decreases during prevention studies, including HIV vaccine trials (2) and chemoprophylaxis, whether post-exposure (3, 4) or pre-exposure (5).

Contrary to the authors' assertion, the annual cost of treatment cited would dwarf prevention research budgets when multiplied out to lifelong commitments. According to their calculations, provision of antiretroviral treatment for newly infected participants in current trials alone would cost \$1,783,518 or \$1,053,897 annually. Because treatment will need to be sustained lifelong once begun, the total cost is in fact more than 20 to 30 times this amount. Additionally, we can anticipate a minimum of 8 to 10 new HIV prevention efficacy trials beginning enrollment in the next 2 to 3 years, including evaluation of microbicides, pre-exposure prophylaxis, and vaccines. Prevention research resources are barely sufficient to pay for the costs of the research, which includes provision of standard prevention for all participants, medical evaluation, safety laboratory testing, HIV testing, recruitment, retention, and community education and participation. In many places, research monies are used to treat sexually transmitted infections and adverse events related to study participation.

Diverting prevention research funds to treatment programs would limit the speed with which promising prevention strategies can be evaluated and more infections averted. Additional ethical and logistical issues would arise from requirements that researchers take primary responsibility for ensuring that treatment is available for trial seroconverters, rather than helping to strengthen treatment programs for everyone. Would this coverage extend to persons found to be infected before enrollment? To persons who become infected after the trial ends? Would treatment for spouses/partners be available, and if not, would drug sharing occur? How would care be provided to those who move away? Because the majority of HIV care is required many years after seroconversion, new financial mechanisms would be needed to assure funds were available when needed. These financial mechanisms would provide no benefit to people with HIV who need treatment now, nor to those who choose not to participate in research.

Effective prevention is the only hope for sustainable universal treatment. Success in the fight against AIDS depends on mutually enabling cooperation between prevention and treatment advocates.

Letters to the Editor

Letters (~300 words) discuss material published in *Science* in the previous 6 months or issues of general interest. They can be submitted through the Web (www.submit2science.org) or by regular mail (1200 New York Ave., NW, Washington, DC 20005, USA). Letters are not acknowledged upon receipt, nor are authors generally consulted before publication. Whether published in full or in part, letters are subject to editing for clarity and space.

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Responding to Amphibian Loss

IN THEIR POLICY FORUM “CONFRONTING amphibian declines and extinctions” (7 July, p. 48), J. R. Mendelson III and colleagues offer a strategy for “stopping” the widespread losses of frogs, toads, and salamanders. Disease research and captive breeding figure prominently in their call for action.

Mendelson *et al.* imply that the main challenge, apart from curbing “familiar threats” such as habitat destruction, lies in combating the chytrid fungus *Batrachochytrium dendrobatidis*. This pathogen may well be a central proximate cause of mortality, but we question the belief that it spreads gradually across large regions, spelling doom for amphibian communities wherever it arrives (1–4). The observations that ostensibly support this “extinction-wave” model are open to interpretation, and the chytrid inhabits many places where major losses have not been observed (5–8). Furthermore, evidence suggests that climate change and other factors may contribute to declines by triggering disease outbreaks, which might travel varying distances in wave-like patterns (9–12). In any case, many populations survive such episodes (13) yet face an uncertain future as environments deteriorate, regionally and globally.

Protecting populations in centers for captive breeding may evoke Noah’s ark. In reality, these centers would be high-tech lifeboats, costly and of uncertain design, afloat indefinitely on perilous seas. Of the species that would obtain the inevitably limited seats, how many would make it home

again, or have a home worth returning to? Of course, some captive breeding is worthwhile, especially for research and education, but its efficacy in preserving nature should not be oversold.

There is no substitute for putting the Earth on a safe path. The Amphibian Conservation Action Plan recognizes this—stating, for example, that global warming must be addressed, and proclaiming amphibians “canaries in the global coal mine” (14). Mendelson *et al.*, however, say nothing about stemming environmental deterioration (besides habitat loss) and would instead put the canaries under intensive care. To suggest that this alone can halt the extinctions undermines scientific credibility and engenders false hope and complacency among voters and consumers.

Biodiversity loss warns that humanity’s life-support system is crumbling. Those who realize this may become responsible global citizens, demanding sound governance and accountability. Through outreach, we must foster an international “war on environmental deterioration” with initiatives on the scale of the Manhattan and Apollo projects. Society faces critical choices, and the clock is running.

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Response

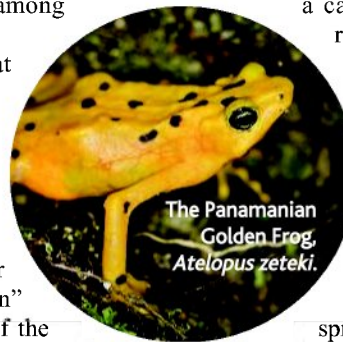
THE AMPHIBIAN CONSERVATION ACTION Plan (ACAP) reflects the need for a global, comprehensive response to amphibian extinctions and is a consensus position reached by 76 international scientists and conservationists (including two of the Letter’s authors, Pounds and Carnaval).

Our Policy Forum identified chytrid-iomycosis [caused by the fungus *Batrachochytrium dendrobatidis* (*Bd*)] as a case study because of its recent emergence, global distribution, and ability to cause extinction. We argued that captive husbandry is a necessary and timely response to this threat.

Pounds *et al.* (i) disagree with some spatio-temporal dynamics of *Bd* spread, not mentioned by us; (ii) are skeptical about captive breeding programs; and (iii) suggest that a focus on captive breeding would distract from other solutions to amphibian extinctions.

Pounds *et al.*’s citations (1–4) do not support their statement that where chytrid fungus is present, there are no major declines because these articles all report declines potentially attributable to chytrid-iomycosis. The loosely worded statement that “many populations survive such episodes” misrepresents the severity of declines. Strong evidence demonstrates that *Bd* is one of the few diseases capable of causing extinction of species (5), not just population extirpation. Nevertheless, we readily acknowledge instances where *Bd* was detected but where amphibian populations were little affected (6).

Pounds *et al.* exaggerate our focus on captive programs and suggest that captive programs “engender false hope and complacency among voters and consumers,” yet they offer no empirical support for these claims or provide alternative actions. Captive programs are a single tool representing a case-specific response that can forestall extinctions (7). Control of *Bd* in the wild is not currently possible, but it is likely to continue causing extinctions of amphibians; these realities warrant captive assurance colonies as a last resort for species



The Panamanian Golden Frog, *Atelopus zeteki*.

endangered by this disease.

We did not say that conservation should focus solely on chytridiomycosis, nor rely solely on captive programs. We endorse the ACAP Declaration, which clearly provides research and conservation priorities for all threats to amphibians.

We disagree with the vague call to reverse environmental deterioration “[t]hrough outreach” as a solution to amphibian extinctions. First, dealing with both the proximate and ultimate causes of amphibian extinctions is the most effective strategy. Pounds *et al.* seem to think that only addressing ultimate causes will prevent ongoing extinctions, but we disagree because many amphibians will go extinct before the global environment responds (8). Second, focused, forward-thinking plans are encouraging to the general public, policy-makers, and donors. Since publication of our Policy Forum, the ACAP has received endorsement from IUCN, unsolicited gifts from foundations, queries from the public, and coverage in the popular media. This attention broadly supports amphibian conservation, not specific causes or programs.

Both groups agree that “war on environ-

mental deterioration” would address the amphibian crisis, and that the clock is running, but even under the best-case scenario, that is a decades-long project, during which time many additional species may be lost (9). Our Policy Forum and ACAP offer specific, large-scale, immediate responses to conserve amphibians.

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