Correspondence

Sustainable Super-Sprinkle: Powdered Local Foods

Stacia Nordin

I appreciate Zlotkin and colleagues' years of work on the Sprinkle product, and it sounds like the product is much improved from the pill form of micronutrient treatments [1]. I'm not at all opposed to Sprinkle-type products or other nutrient pills for treatment (or in other special situations), but as ten years of international work experience on food and nutrition security issues has shown me, few programmes are supporting local solutions to problems. Once again, a message is being sent that nutrition comes from a pill or packet, made by a foreigner, and requires money.

In the case of Sprinkles, the product could support local solutions by including a message on each sachet about the importance of eating a wide variety of local foods—or a picture of local fruits, vegetables, and legumes. Instead of just sprinkling a packet onto a bulky carbohydrate food, use the Sprinkles as treatment along with instruction about planting and eating less of that bulky carbohydrate in the first place. Even better would be to take all that research, time, energy, and money to teach people (or local manufacturers) how to make their own Sprinkles from local nuts, fruits, greens, oilseeds, insects, fish, and the like.

The results could be just as immediate and dramatic, but with an impact that could last for generations to come. The organisations that support this type of permanent intervention could be mentioned during every teaching session along with big banners and flyers that announce them as the inventors and/or supporters. Just imagine a nice sprinkle powder that everyone can have on hand to improve their own nutrition without relying on a packet from an outside source that is manufactured with machines and jetted in with thousands of litres of petrol (or trucked across the country, if it is made in country).

I'm sure that pre-packaged, imported products have their place in wars, tsunamis, a few cities, and other disasters, but for the majority of the 750 million children in the developing world, their own indigenous foods would have just as much effect, with a longer-term impact on the society's nutritional health.

I saw Zlotkin's presentation on Sprinkles at the International Congress of Dietetics conference in Chicago, Illinois, in 2004, and he did include a sentence about diversifying diets as part of the whole project, but it was strongly overshadowed by discussion of bringing in external resources and experts. When I asked him about using the same resources that went into developing, manufacturing, and transporting Sprinkles to create a local sprinkle product with an emphasis on local diversified diets, he immediately responded that it wouldn't work.

How do we know, if no one really puts the effort into it at the level that products like Sprinkles get?

I've posted this message to several food and nutrition listservs and magazines, and I am now beginning to learn of some small projects working towards local sprinkle products. Zlotkin and team could assist these projects to research the work and scale it up to other countries with other local foods. ■

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Citation: Nordin S (2005) Sustainable super-sprinkle: Powdered local foods. PLoS Med 2(7): e188.

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Authors' Reply: Sprinkles as a Home Fortification Strategy to Improve the Quality of Complementary Foods

We are writing in response to the letter by Stacia Nordin [1]. Independent of where a child is born in the world, the most appropriate feeding regimen is breast milk until six months of age, followed by a weaning or complementary food [2]. It is known that breast milk provides all the essential nutrients for a growing infant, except for vitamin D. It is also known that complementary foods should contribute to providing all of the essential nutrients when breast milk is no longer the sole source of nutrition after the first few months of life. However, as early as 1930, it was realized that typical complementary foods were generally poor sources of micronutrients (minerals and vitamins) and were often not sufficient to meet the micronutrient needs of growing children. For example, per 100 g, rice-based complementary foods contain about 1 mg of iron, and wheat-based complementary foods contain about 0.8 mg of iron [3]. Even a meat-based complementary food, such as commercial "toddler beef stew", contains only 1.2 mg of iron in each 170-g jar. Since the recommended dietary allowance for iron is 11 mg/day (for ages 7–12 months) [4], clearly a rice- or wheat-based complementary food, or even a dilute meat-based stew, would not provide an adequate amount of iron for a growing infant.

Pablum, the first fortified baby food, was invented at the Hospital for Sick Children in Toronto, Canada, in the 1930s [5]. Subsequently, by the early 1960s in North America, all commercially manufactured infant cereals were fortified with iron. Today, the major source of iron in the diet of a North American child is fortified commercial infant cereals. And, indeed, the low rates of iron-deficiency anaemia in Canada and the United States are thought to be partly a result of the widespread use of commercially available iron-fortified cereals [6].

Another good example of a fortified food for young children in North America is fluid milk products, which are fortified with vitamin D in order to prevent the development of rickets. It is currently well accepted among nutritionists and pediatricians that most young children in North America depend on fortified foods to meet their micronutrient needs.

In most developing countries, access to commercially processed baby foods (fortified with iron) is very limited

mainly because of their high cost and limited availability [7]. It is noteworthy that recent research has demonstrated that even if dietary diversification and modification (such as soaking, fermentation, and germination) strategies are used at the household level, they may not be sufficient to overcome the deficits in iron and other micronutrients [3]. As a result, other options need to be considered for young children living in developing and poor countries to ensure that all of their nutrient requirements are met [8]. The use of Sprinkles is one such option [9,10]. One of the greatest advantages of the Sprinkles concept is its emphasis on complementary food consumption because Sprinkles have to be mixed with food. When educating caregivers about anaemia and the use of Sprinkles, healthy weaning practices can be concurrently promoted to ensure the timely introduction of complementary foods at six months of age in addition to continued breast feeding (as recommended by the World Health Organization) [2]. This is an important benefit, as it is well known that in many developing countries poor weaning practices are common [3]. As a home fortificant, Sprinkles ensure that the food eaten contains adequate amounts of essential micronutrients. Indeed, Sprinkles are meant to improve the nutritional value of homemade baby foods, which are otherwise poor in micronutrient content. Sprinkles can enrich foods not only with iron but also with other essential micronutrients such as zinc, folic acid, and vitamins A and C. In addition, since Sprinkles can be easily mixed with any homemade semisolid foods, their use does not require any change in food practices; thus, they can be easily accepted in diverse cultural settings.

With anaemia rates as high as 80% in young children in some developing countries, current food-based strategies alone are clearly not effective. All children should have the right to eat foods that meet their nutritional needs. The use of Sprinkles is one way to help these children meet their nutrient requirements. Unfortunately, a food-based strategy alone, using locally available unfortified foods, in most circumstances, is simply inadequate and may further predispose a growing child to various micronutrient deficiencies [8]. ■

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Citation: Zlotkin SH, Schauer C, Christofides A, Sharieff W, Tondeur MC, et al. (2005) Authors' reply: Sprinkles as a home fortification strategy to improve the quality of complementary foods. PLoS Med 2(7): e202.

Competing Interests: SHZ is an occasional consultant to Bristol-Myers Squibb, and Mead Johnson. He owns the intellectual property rights to Sprinkles. The H. J. Heinz Company is supporting the technical development of Sprinkles on a cost-recovery basis. Any profit from royalty fees on the technology transfer of Sprinkles is currently donated to the Hospital for Sick Children Foundation.

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Bold Suggestion by Smith

David Cohen

Richard Smith's key suggestion [1] is that medical journals "should stop publishing trials" and concentrate on "critically evaluating them." This bold and radical suggestion deserves wide debate. It's obvious that many medical journals are losing relevance as vehicles for scientific information, but it's unclear what will save them. Even as journals strive to better enforce their conflicts-of-interest disclosure rules, drug companies will strive to find or create other publication outlets that can communicate to physicians precisely what advertisers wish to communicate. In sum, an unanticipated effect of purging clinical trial reports from medical journals might be an even larger proliferation of frank advertising outlets and messages that might more effectively catch doctors' attentions. ■

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Reference

1. Smith R (2005) Medical journals are an extension of the marketing arm of pharmaceutical companies. PLoS Med 2: e138. DOI: 10.1371/journal.pmed.0020138

Citation: Cohen D (2005) Bold suggestion by Smith. PLoS Med 2(7): e226.

Competing Interests: DC is a former editor of *Ethical Human Sciences and Services*, which published several articles critical of the drug industry, and has authored articles critical of drug industry sponsorship and influence on clinical psychopharmacology trials.

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Medical Journals, Academia, and Industry-Sponsored Clinical Trials

Valeria Frighi

Sadly, I fully agree with Richard Smith's opinion [1] that many medical journals have become marketing offices of pharmaceutical companies. Even worse is that few people seem to realize this, and there are many respectable academics who would wholeheartedly dispute these views. The "psychology of gift" operates in every social environment, being so pervasive because it is based on the profoundly human and universal norm of reciprocity [2,3]. In academia and medical publishing it produces great returns to the pharmaceutical industry via clinical scientists who are not dishonest but in a state of denial about their motivations, as Jerome Kassirer, former editor of the *New England Journal of Medicine*, describes very clearly in his recent book [4]. What is happening is also extremely serious because the tainted trials we are offered can make evidence-based medicine a pointless enterprise. Again, something not widely appreciated.

I think Smith's suggestions that there should be more public funding for clinical trials and that journals should critique rather than publish the results of the trials are very interesting. However, how are we going to get publicly, and adequately, funded trials given the current financial climate?

A practical alternative to Smith's suggestion is to play one pharmaceutical company against the other in head-to-head trials, an approach that can help retain independence and that has been used to this purpose before. Another strategy would be for either the regulatory authorities or the academic review boards to demand of the pharmaceutical companies that whenever a new drug is tested in a phase III trial, it should always be done not only against placebo but also against the drug that the condition is generally treated with. This active comparator must be used at the appropriate dose, namely neither too low nor too high (in order to avoid the tested drug spuriously seeming more effective or safe). Moreover, any new licence should be accompanied by a legal requirement for a stringent system of post-marketing surveillance, to be run by the drug company but overviewed by the regulatory authority.

These strategies could possibly help produce results that are more reliable from a scientific point of view, help reduce the number of expensive but not innovative "me too" drugs, and help protect patients' safety more efficiently.

Lastly, I hope Richard Smith will go straight into the lion's den and send his thoughts not only to the similarly minded editors and readers of *PLoS Medicine* but to some of the journals who are the most culpable of the policy he is exposing. ■

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Citation: Frighi V (2005) Medical journals, academia, and industry-sponsored clinical trials. PLoS Med 2(7): e218.

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Might Banning Trial Publication Do More Harm Than Good?

David Sackett

Smithereens are better than no Smith at all. It was grand to see Richard Smith in full flight again [1], a raptor this time, relegating the randomized controlled trials he previously championed in the *BMJ* to the ether, to be replaced by printed "commentaries." In doing so, he laid three problematic eggs. First, he shoved systematic reviews and meta-analyses, surely the least biased summaries of efficacy, out of the nest before he took off. Second, the canaries who write commentaries often live in gilded cages provided by the drug industry and printing their pronouncements would make matters worse. Finally, the fledglings who conduct nondrug health-care trials, especially in low- and middle-income countries, shouldn't have their careers stunted by not being able to publish their work in print journals. ■

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1. Smith R (2005) Medical journals are an extension of the marketing arm of pharmaceutical companies. PLoS Med 2: e138. DOI: 10.1371/journal.pmed.0020138

Citation: Sackett D (2005) Might banning trial publication do more harm than good? PLoS Med 2(7): e220.

Competing Interests: DS has been wined, dined, supported, transported, and paid to speak by countless pharmaceutical firms for over 40 years, beginning with two research fellowships and interest-free loans that allowed him to finish medical school. Dozens of his randomized trials have been supported in part (but never in whole) by pharmaceutical firms, who never received or analysed primary data and never had veto power over any reports, presentations, or publications of the results. He has twice worked as a paid consultant to advise pharmaceutical firms on whether their products caused lethal side effects; on both occasions he told them yes. He has testified as an unpaid expert witness for a patient with stroke who successfully sued a manufacturer of oral contraceptives, and as a paid expert in preparing a class-action suit against a manufacturer of prosthetic heart valves.

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Little Fish Are Less Likely to Take the Bait

Harvey Marcovitch

One solution for fair-minded doctors not mentioned by Smith [1] might be to keep away from major high-impact

journals and subscribe instead to those with a lower profile but that serve their specialty. I analysed all original papers published in the last 12 issues of *Archives of Disease in Childhood*. Of 198 such papers, there were seven (3.5%) manufacturer-funded studies dealing with drugs, vaccines, or infant foods. Another ten papers (5%) dealt with drugs or vaccines, including three reports of adverse events, but were not funded by industry. The funding of one was obscure. This pristine record was somewhat spoiled by a sponsored supplement, but clearly labelled as such, about a particular medication. It provoked an angry correspondence on the subscribers' message board of one of the co-publishers. It seems that at least paediatrics, a far-away specialty of which Smith may know little, treads a careful path. ■

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1. Smith R (2005) Medical journals are an extension of the marketing arm of pharmaceutical companies. PLoS Med 2: e138. DOI: 10.1371/journal.pmed.0020138

Citation: Marcovitch H (2005) Little fish are less likely to take the bait. PLoS Med 2(7): e221.

Competing Interests: HM was Editor of *Archives of Disease in Childhood* for nine years, and is now Associate Editor for the *BMJ*. He has no pharmaceutical company sponsorship.

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Focus on the Funding and Production of Evidence Rather Than Its Publication

Trevor Sheldon

Richard Smith has correctly highlighted the potential distortion of the evidence base caused by the publication of commercially sponsored trials [1]. However, his proposed solution could do with more thought.

First, let us be clear that the problem is possibly much wider than drug-company trials. There is the risk of systematic bias in reports of any research funded by a body that has an interest in the results. This "sponsor-induced bias" has been well documented in the area of tobacco-company-funded research on the effects of direct and indirect smoking [2]. In addition, governments, charities with an interest in a disease, and other bodies may also help to ensure that the results of research they sponsor (including trials) or the reporting of research favour one particular outcome. Lastly, individuals who carry out research, even if not funded by an interest group, may also bring prejudices to the table that influence the results and the published report. In other words, the tendency to bias is omnipresent. The issue of commercially funded trials is simply one of the degree and influence that trials have on clinical practice and health-care spending.

Following Smith's thinking to its logical conclusion, we would not publish any research but simply critiques. Smith proposes that instead of publishing trials, journals should concentrate on critically describing them. If he is not confident that the current system of peer review is sufficiently robust to identify weaknesses, why should he be any more confident in the critiquing process (which is a form of peer review)? Journal peer review is often ad hoc (especially when my work is rejected) and is in desperate need of professionalizing, but I suspect along with Smith that this is not sufficient protection. Surely the way to deal with the systematic risk of bias is a reform not in the publication but in the production of evidence, which in turn reflects the way it is funded, conducted, analysed, and reported.

My alternative solution in the case of trials is as follows. Companies (or indeed any body with a particular interest) should not be allowed to directly fund a clinical trial and no journal should publish a company-sponsored trial. Instead industry should pay a public or independent trials body, staffed by the best methodologists around and possibly established on an international scale. This international infrastructure should be publicly funded so that its staff do not feel dependent on industry business for security. The body, in conjunction with clinical experts from around the world, should conduct the study, ensuring that the questions are in the public's interest and fair (consumers would have an important role to play here).

This infrastructure would ensure that the research was of the highest standard and reported accurately. Once the funding had been agreed on, there would be a compulsion to register the trial and to publish no matter what the results. This body would also have the ability to carry out or commission economic modelling (which is even more susceptible than trials to sponsor-induced bias) [3]. The resulting data would be held in a publicly accessible data archive. We should have an international agreement that no phase III trials would be permitted other than through this route. While still a rather bureaucratic response, it would ensure that the evidence base was less contaminated. Drug companies might even find that such a social solution results in trials being cheaper and easier to run. ■

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Citation: Sheldon T (2005) Focus on the funding and production of evidence rather than its publication. PLoS Med 2(7): e222.

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Bitter Pills and Puffed Trials

Stephen Senn

I agree with Richard Smith [1] that something needs to be done about the reporting of pharmaceutical industry trials. Like him, I believe that the solution should include compulsory publication on the Internet of trials [2]. However, I disagree that the problem has its origin with the pharmaceutical industry; it is inherent to medical publication.

Of his eight ways of massaging data, the last five are dealt with by the International Conference on Harmonisation guidelines covering statistical principles for clinical trials (ICH E9) [3] that require prespecification of analyses. It is not possible to claim noninferiority on the basis of failure to prove a difference, and a paper describing appropriate approaches to equivalence trials that Richard Smith thought worth publishing in the *BMJ* [4] was doing no more than explaining what was common practice within the industry. The first three points are less easily policed, although choice of control group is taken extremely seriously, and, indeed, there is an appropriately entitled guideline [5] that covers this.

The problems are inherent to publication not drug regulation. An instance: the *New England Journal of Medicine* published in January 2002 a paper claiming that voriconazole is a suitable alternative to amphotericin B preparations for empirical antifungal therapy in patients with neutropenia and persistent fever [6]. However, a letter to the editor in the same issue of that journal from scientists based at the United States Food and Drug Administration [7] pointed out that the analysis presented was not what was prespecified in the protocol and that not only had voriconazole failed to demonstrate noninferiority, but it was actually statistically significantly inferior to amphotericin B. Surely, responsibility for this discrepancy cannot be laid at the door of the Food and Drug Administration, nor can it be blamed on Pfizer. Rather, the authors and the *New England Journal of Medicine* owe readers some sort of explanation.

Do the editors agree with Richard Smith (and me) that a published paper, whatever else it covers, should always identify the results of prespecified analysis, and if so, how do they check that this is so?

Thus, I agree with Richard Smith that much is wrong with the publication of clinical trials sponsored by the pharmaceutical industry. I disagree that it is a particular problem for industry trials. It is the publication process that is in need of reform, and in particular we need to scrutinize carefully the motives of authors in publishing and the standards that editors apply in deciding what gets published. ■

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Citation: Senn S (2005) Bitter pills and puffed trials. PLoS Med 2(7): e219.

Competing Interests: SS has consulted for Actelion, Alcon, Amgen, Astra (now Astra-Zeneca), Astra-Zeneca, Aventis, Auxilium, Biosyn, Boehringer Ingelheim, Bracco, Bristol-Myer Squibb, Chiesi, Chiron, Ciba-Geigy (now Novartis), Covance, Dexcel, Elan, Eli-Lilly, Fournier, Glaxo-Wellcome (now GSK), GSK, INO Therapeutics, Janssen, Johnson&Johnson, Jouveinal (now Pfizer), Leiras, Merz, Novartis, Novartis Consumer Health, Novartis Ophthamology, Numico, Orion, Pleaid, Pfizer, Pharmacia (now Pfizer), Pharmapart, Phocus, Roche, Sandoz (now Novartis), Sanofi, Servier, Schein, Schering AG, Shire, Smith-Kline Beecham (now GSK), Statwood, Strakan, Wyeth, Zeneca (now Astra-Zeneca) and possibly other companies he has forgotten about. He used to work for Ciba-Geigy and in consequence owns some shares in Novartis. This note has been prepared without consulting any of the above companies, without their knowledge, and without their express permission, and none of his views should be attributed to any of the above. SS is an academic whose career is furthered by publishing. His views should also not be ascribed to his current employer, Glasgow University.

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Editors' Reply

Steven Senn [1] raises several very important points about the publication of trials. In an attempt to improve transparency of reporting, we require authors to submit their protocol along with the trial so that it is available for reviewers and editors to compare with the journal article, and we encourage the protocol to be published with the trial so that readers can check these results for themselves. One problem in trial reporting is the relatively unstructured nature of trial reports in medical journals compared with, for example, Trial Bank (http://rctbank.ucsf.edu/). We are currently considering how we report trials at PLoS; a much more structured and, hence, more transparent report may make it much harder to hide results (or the lack of them). ■

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Reference

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Citation: Barbour V, Cohen B, Yamey G (2005) Editors' reply. PLoS Med 2(7): e225.

Competing Interests: The authors are editors for *PLoS Medicine*.

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A Further Response to Shah Ebrahim

Michael Makover

Shah Ebrahim says, in his answer to my statement in our debate [1], that plaque is so common that it makes sense to treat only those likely to have an acute event in the near future. Not everyone has a heart attack but everyone ages, nor can we be sure who will be lucky as they age and who will not.

Anyone with a low-density lipoprotein level above 70 mg/dl is at risk [2]. Narrowing of arteries must certainly contribute to health decline in aging. He says that most plaque is stable and does not rupture. The half-million people who have a heart attack and the hundreds of thousands of individuals who have a stroke in the United States alone each year would disagree. Waiting decades more for further studies will not help all those now succumbing to the disease, as long as all the components have already been well vetted, as they have been. Ebrahim's statement that "most [plaques] are stable and unlikely to rupture" is based on his own study published in *Stroke* [3], but the paper has no data relating to how many patients found to have increased intima-media wall thickness (IMT) or plaque actually had heart attacks or strokes. It did find that intimal-wall changes were highly associated with ischemic heart disease.

It is correct that risk factors can predict heart disease and stroke to some degree, though I have many patients for whom that approach fails while IMT detects the risk otherwise missed. However, risk factor analysis is not enough. Changes in smoking, diet, weight, blood pressure, and such are all targets for treatment, but how do doctors know whether they have controlled them adequately? If IMT increases, more control is required. If IMT stabilizes or reverses a little, then it means that control is at goal. Family history of premature coronary artery disease is a major but underused risk factor. The causative factors have not yet been elucidated by research, so we do not know what the goals are. However, IMT provides a highly satisfactory parameter by which to judge the effectiveness of treatment in familial coronary artery disease: IMT stabilization and reversal are good, whereas progression is bad and requires more intensive measures.

Epidemiology and public-health planning correctly look at policies to apply to large populations. However, the practice of medicine is patient by patient, accomplished in the face-to-face doctor–patient relationship. Policy can be useful as a resource, but each patient should have the maximum individualized care and access that a doctor can provide. Patients should be able to make their own informed choices and not be dictated to by policies meant for masses. Shouldn't everyone with increased IMT at least be informed of the options available to limit it rather than waiting until acute events or advanced narrowing occur? It would be best to start a healthy lifestyle from birth, but fortunately by adulthood there is still time to make an enormous difference in practical terms if we take action at the stage when intimal widening is detectable with the highly sensitive ultrasound described in my original viewpoint [1]. ■

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Citation: Makover M (2005) A further response to Shah Ebrahim. PLoS Med 2(7): e189.

Competing Interests: The author has declared that no competing interests exist.

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Author's Reply

In response to Michael Makover's comments [1], the important point at issue here is *evidence*—and not whether there is room for both population approaches and high-risk approaches. We can certainly identify plaques using carotid ultrasound. We can use risk factor scoring schemes to identify those at high risk of suffering a cardiovascular event. We can give patients a range of drugs that have been shown in trials to reduce risk of these events. However, the relevant evidence from randomised controlled trials of risk factor screening (using either scores or carotid ultrasound) and intervention is simply not available. So what do we do—ignore the lack of evidence? Or do we get on with organising the trials? ■

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Applause to *PLoS Medicine* for Initiating Student Forum

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We congratulate and acknowledge *PLoS Medicine* for initiating a students' forum [1] and for its efforts to encourage students' participation across the globe. There is really a need for medical students, especially from the developing world, to be actively conducting research, reading journals, publishing papers, and staying in touch with current developments in the field of medicine. Many developing countries lack a national-level student medical journal for students to exchange their views and ideas, which thereby pacifies their thinking and makes them hypnotic to issues such as the influence of drug companies and the neglected health problems of poorer countries.

It will be really motivating for students from developing countries to actively take part in debate through the Student Forum of *PLoS Medicine*, which is composed of articles selected by student representatives across the world. The unique integration of student associations with *PLoS Medicine*, and the journal's policy of not publishing advertisements for drugs or medical devices, will also enlighten students about

the influence of drug companies in medical practice and enable students to realize their priorities in poorer countries for the future. Thereby, students may focus their attention on becoming professionals in developing new strategies to combat killer infectious diseases like malaria and tuberculosis, and malnutrition—such as vitamin deficiencies among children and iron deficiency among pregnant women—that are dreaded and very common in poorer countries. ■

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