Which Risk Factors Matter to Whom?

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There is a much-quoted saying, attributed to the epidemiologist Geoffrey Rose: "A large number of people exposed to a small risk may generate many more cases than a small number exposed to a very high risk." This is true for many individual risk factors such as salt intake (linked to high blood pressure and cardiovascular disease) and speeding on the highway (linked to injuries and accidents). Does it apply to many other global health risks? The study by Anthony Rodgers and colleagues suggests that it does.

To develop effective health policies, one must understand the existing health risks and disease burdens. On a worldwide scale, this is a tough challenge. The Global Burden of Disease Database, maintained by the World Health Organization (WHO), collects data from countries around the world on risk factors such as tobacco, malnutrition, childhood abuse, unsafe sex, childbirth, and cholesterol levels, as well as on disease burdens, for example depression, blindness, and diarrhea. A large group of scientists from all over the world has developed a framework to analyze these data. To compare different risks or burdens, they calculate disability-adjusted life-years, or DALYs—the number of healthy life years lost because of a particular disease or risk factor.

Rodgers and colleagues used data from the WHO database for 26 risk factors and from 14 epidemiological subregions of the world to calculate the proportion of risk-factor-attributable disease burden in different population subgroups defined by age, sex, and exposure level.

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Tobacco is a major player in the global burden of disease (Photo: Bill Branson)

For being underweight in childhood, for example—the leading risk factor for global loss of healthy life—they found that only 35% of the disease burden occurred in severely underweight children, the rest occurred in those only moderately underweight. The relative risks for the moderately underweight are much lower, but the number of children in that category is so large that the total attributable burden amounted to almost two-thirds of the total global burden of disease for that risk factor.

The analysis confirms—and extends to a global level—previous research showing that many major health risks are important across the range of exposure levels, not just among individuals exposed to high levels of risk. It also points to risk factors that are particularly prevalent among specific populations and age groups, and for which highly targeted interventions could be effective.

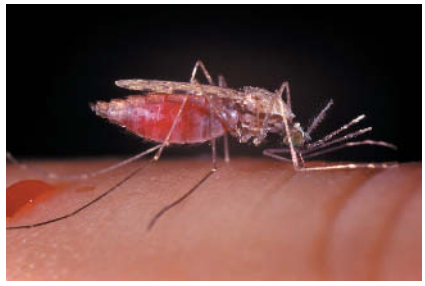
Despite numerous caveats and limitations of studies like this one, such analyses are essential aids in guiding the distribution of limited funds to lower the burden of life years lost to premature death and disability.

Rodgers A, Ezzati M, Vander Hoorn S, Lopez AD, Lin RB, et al. (2004) Distribution of major health risks: Findings from the Global Burden of Disease study. DOI: 10.1371/journal.pmed.0010027

Getting the Fluid Balance Right in Malaria

DOI: 10.1371/journal.pmed.0010024

Acidosis is a major cause of death in patients with malaria, although what causes acidosis is still unclear. One possibility is that hypovolemia contributes to the problem, and that rehydration therapy could be of benefit. Now, Sanjeev Krishna and colleagues have shown that in children with severe malaria dehydration is not severe and is not correlated with other measures of disease severity. "The optimum resuscitation approach in severe childhood malaria remains to be defined," says Nick White (Mahidol University, Thailand), the academic editor of the paper. "The relative advantages of blood, colloids, and crystalloids need to be characterized."



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Anopheles gambiae, the principal vector of malaria (Photo: Jim Gathany)

Every year around 200 million people worldwide contract malaria, of whom over a million die. The vast majority of those who die are children under five years, mostly in Africa, since young children have had little chance to acquire any immunity. Fluid resuscitation is generally considered to be a cornerstone of treatment—but how much fluid should be given? Some researchers believe that surrogate signs of fluid depletion—such as tachycardia, reduced capillary refill time, and reduced urine excretion—suggest that there is substantial volume depletion. The reason that the amount of fluid given matters so much is that giving too much, especially of hypotonic solutions, can lead to electrolyte imbalance, especially hyponatremia and hypokalemia.

Research efforts have been hampered by not having an easy way to assess in patients the fluid depletion in different compartments of the body, i.e., total body water and extracellular and intracellular water volume. Krishna and colleagues used heavy-water distribution to calculate the total body water and bromide distribution to determine the extracellular volume in 19 children with moderately severe malaria and 16 with severe malaria in Gabon. By subtracting extracellular volume from total body water, they were able to calculate intracellular volume for each child. They also used a less invasive and more rapid method of determining water volumes based on using bioelectrical impedance to calculate the volume.

None of the children were severely dehydrated (defined as more than 100 ml/kg depletion), and only three of the children with severe anemia had fluid depletion, which was moderate (60–90 ml/kg depletion). "This challenges the

view that dehydration is a major contributor to the pathology of this frequently lethal disease," says White.

So based on these data, obtained from a carefully studied, albeit small group of children, what should people who treat children with malaria do? The authors' first recommendation is that clinicians should think again about how vigorously they rehydrate children, and if they have access to ways of assessing fluid volume more precisely, they should do so (not a trivial undertaking in many hospitals where these children are treated). And certainly the methods used by Krishna and colleagues should undergo wider testing in larger groups of children to confirm their usefulness. Until the worldwide efforts to prevent malaria come to fruition, refining the management of infected children will remain a cornerstone of the efforts against this devastating disease.

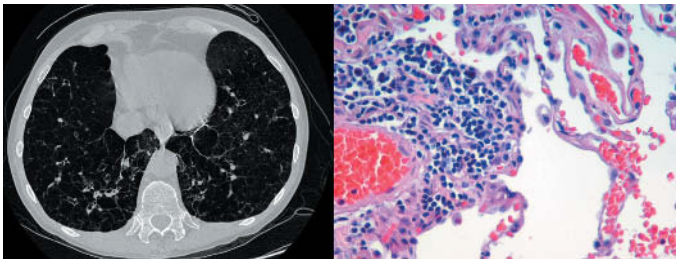
Planche T, Onanga M, Schwenk A, Dzeing A, Borrmann S, et al. (2004) Assessment of volume depletion in children with malaria. DOI: 10.1371/journal.pmed.001001

T Cells Cause Lung Damage in Emphysema

DOI: 10.1371/journal.pmed.0010025

T lymphocytes may have an important role in the pathogenesis of smoking-related emphysema, according to a new study by researchers from Houston, Texas, United States. "We now know that T cells are not only present in chronic obstructive pulmonary disease [COPD], but are harmful," comments Steven Shapiro from Brigham and Women's Hospital, Harvard Medical School, who was not involved in the study. "We also now have a pathway that could be interrupted to prevent lung destruction in COPD."

Farrah Kheradmand and colleagues took lung samples from 28 ex-smokers who had been admitted to hospital for lung resection: 18 patients had moderate to severe COPD as well as evidence of emphysema, and ten patients had none. The researchers isolated lung lymphocytes from the samples and used two-color flow cytometry to phenotypically characterize the cells. They found that



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CT image of the lung of subjects with end-stage emphysema next to a photomicrograph of their resected lung stained with H&E

lymphocytes taken from patients with emphysema expressed more CCR5 and CXCR3 receptors, which are associated with a particular type of T cell called T helper 1 (Th1), than did those from control individuals. By contrast, expression of CCR4 receptors, which are found on T helper 2 (Th2) cells, was very low in both control and emphysema groups.

In a separate experiment, Kheradmand's team showed that lung lymphocytes taken from patients with emphysema secreted more of three other proteins—interferon gamma, monokine induced

Different HIV Drugs Cause Different Lipid Profiles

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Nevirapine and efavirenz are the most commonly prescribed of the class of antiretroviral drugs called non-nucleoside reverse transcriptase inhibitors (NNRTIs). Efavirenz has the advantage of once-daily dosing. In a recent study called the 2NN study (Lancet 363: 1253–1263), it appeared to be only marginally superior to nevirapine in terms of clinical success and virological suppression. Van Leth and colleagues have now shown that while nevirapine and efavirenz both raise high-density lipoprotein (HDL) cholesterol (the "good" type of cholesterol), the overall lipid profile is better with nevirapine than with efavirenz.

"These data suggest that nevirapine may be preferable to efavirenz in HIV-infected adults with other cardiovascular risk factors," says the study's academic editor, Andrew Carr of St. Vincent's Hospital in Darlinghurst, Australia. "However, perceived cardiovascular risk is only one factor that would affect the choice between these two drugs."

Van Leth and colleagues prospectively analyzed the lipids of patients enrolled in the 2NN study, a randomized, open-label efficacy study that included adults with HIV who had never been on antiretroviral drugs. All patients were given stavudine and lamivudine and were then randomized into three treatment groups: nevirapine, efavirenz, or both.

For the lipid analysis, which was preplanned, the researchers included only the nevirapine and efavirenz groups (417 and 289 patients, respectively). This was because the 2NN study showed that simultaneous use of nevirapine and efavirenz should be avoided—the combination is associated with increased toxicity without increased efficacy. The increase in HDL cholesterol was significantly higher with nevirapine than with efavirenz. There was a decrease in the ratio of total cholesterol to HDL cholesterol with nevirapine and an increase with efavirenz.

The study does not prove, however, that the rise in HDL cholesterol seen with NNRTIs (especially nevirapine) actually leads to a reduction in coronary heart disease. "There are no vascular functional data," says Carr, "or clinical vascular endpoint data that confirm that the statistically significant lipid differences observed are clinically significant."

The study was funded by Boehringer Ingelheim, the manufacturer of nevirapine. The authors clearly state that the company had "a nonbinding input on issues of study design and analyses" but it had "no influence on reporting of the data or the decision to publish."

Despite its limitations, van Leth and colleagues' study "moves clinicians and patients away from 'one-size-fits-all' antiretroviral therapy," says Carr. "It takes us further along the path of choice of antiretroviral therapy being individualized according to other patient co-morbidities and risk factors, as well as therapy simplicity and side effects."

van Leth F, Phanuphak P, Stroes E, Gazzard B, Cahn P, et al. (2004) Nevirapine and efavirenz elicit different changes in lipid profiles in antiretroviral-therapy-naive patients infected with HIV-1. DOI: 10.1371/journal.pmed.0010019

by interferon (MIG), and interferon-inducible protein 10 (IP-10)—than control patients. MIG and IP-10 are known to be produced by injured epithelial cells and are ligands for CXCR3 receptors, which are expressed by Th1 cells. Importantly, the researchers were also able to show that isolated peripheral lung macrophages secreted matrix metalloproteinase-12 (MMP12), an enzyme that degrades elastin—a protein important for lung elasticity—in the lungs, in response to IP-10 and MIG. Together these findings, say the authors, indicate that Th1 cells, but not Th2 cells, are required for producing the elastin-destroying lung environment of emphysema.

The researchers now intend to investigate the antigens that drive the Th1-based inflammation that underlies emphysema. "Ultimately, we seek to understand the biochemistry of tobacco smoke that triggers inflammation in the first place, and whether such insight might explain other environmentally triggered lung diseases," explains Kheradmand. "To understand such detailed immune mechanisms, we really need an improved experimental model of disease, and this we are currently working on."

Grumelli S, Corry DB, Song LZ, Song L, Green L, et al. (2004) An immune basis for lung parenchymal destruction in chronic obstructive pulmonary disease and emphysema. DOI: 10.1371/journal.pmed.0010008

Oats Intolerance in Celiac Disease

DOI: 10.1371/journal.pmed.0010023

Most patients with celiac disease can eliminate their symptoms—at a price: life-long adherence to a gluten-free diet. This means no wheat, rye, barley, and, until recently, no oats. Then some recent studies suggested that oats did not cause the intestinal inflammation characteristic of the disease, and thus oats are now often included in the celiac disease diet. This is good news for patients coping with severe restrictions on what they can and must not eat, but a study by Ludvig Sollid and colleagues in this issue of *PLoS Medicine* suggests that oats are not safe in all cases.

Like other chronic inflammatory diseases, celiac disease is caused by a complex interplay between genetic and environmental factors, but it is better understood than most. Long believed to be a relatively rare disorder, it is now thought to affect about one in 250 people worldwide. Clinical symptoms are present in less than half of patients and vary considerably. Genetically, almost all patients have one of two predisposing HLA molecules, which determine the context in which their immune system encounters foreign antigens, including gluten proteins found in wheat and other cereals. In individuals with celiac disease, the immune system mounts an abnormal response to gluten, which is characterized by gluten-reactive intestinal T cells and by inflammation and compromised function of the small intestine.

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The celiac diet excludes many cereal products (Photo: National Cancer Institute)

Ludvig Sollid and colleagues applied the current understanding of celiac disease and a range of molecular pathology tools to studying the response to oats of nine patients with celiac disease. The nine patients were not a random sample: all of them had been eating oats, and four of them had shown clinical symptoms after oats ingestion. The goal of the study was to characterize the intestinal T cell response to oats in these patients, and to relate it to clinical symptoms and intestinal biopsy results. All patients were on a gluten-free diet and ate oats that were free of contamination by other cereals.

Three of the four patients who had reported problems after eating oats showed intestinal inflammation typical of celiac disease, and Sollid and colleagues studied intestinal T cells from these three patients. Two of the five patients who seemed to tolerate oats also had oats-reactive intestinal T cells. Functional study of these T cells showed that they were restricted to celiac-disease-associated HLA molecules and that they recognized two peptides derived from oat avenin that are very similar to peptides of gluten.

Taken together, the findings show that intolerance to oats exists at least in some patients with celiac disease, and that those patients have the same molecular reaction to oats that other patients have to wheat, barley, or rye. However, identical reactions were also seen in two of the patients who were clinically tolerant to oats. The authors suggest that these reactions could develop into symptomatic disease after some time delay, but there is no proof that the presence of oats-reactive T cells is an indicator of future symptoms or even of enhanced susceptibility to clinical oats intolerance.

Oats are not safe for all patients with celiac disease, but future studies are needed to determine the frequency of oats intolerance.

Arentz-Hansen H, Fleckenstein B, Molberg Ø, Scott H, Koning F, et al. (2004) The molecular basis for oat intolerance in celiac disease patients. DOI: 10.1371/journal.pmed.0010001