Questions Regarding the Effectiveness of Trimethoprim-Sulfamethoxazole (Cotrimoxazole) Prophylaxis in African Children

Sir—The publication of Madhi’s study [1] adds valuable information to our understanding of the still-unanswered question of the efficacy of trimethoprim-sulfamethoxazole (cotrimoxazole) for primary prevention of Pneumocystis carinii pneumonia (PCP) in HIV-infected African children. Nevertheless, it may be overstating the evidence to conclude, as the article’s title implies [1], that cotrimoxazole was “ineffective.” Optimally, to determine the protective efficacy of cotrimoxazole, the total number of children at risk must be known, thereby allowing one to directly measure PCP incidence as a function of the total size of the populations that do and do not use cotrimoxazole. Using the definitions shown in figure 1, we can express this mathematically as (a/A)/(b/B). However, the question actually asked in Madhi’s study [1] was quite different: “Of children who already have pneumonia, was PCP more common among those who did or those who did not use cotrimoxazole before becoming ill?” As shown in figure 1, this can be expressed mathematically as (a/c)/(b/d).

This is problematic for 2 reasons. First, the sizes of populations a, b, c, and d (figure 1) do not permit any inferences about the sizes of source populations A and B. Lacking these proportions, no valid conclusions can be made about cotrimoxazole’s efficacy in the entire population of at-risk children. Second, it may be hazardous to assume that PCP-infected children who had taken cotrimoxazole prophylaxis are representative of all children taking cotrimoxazole prophylaxis. We suspect, for example, that prophylaxis failed in many of these PCP-infected children, either because they didn’t take the drug regularly or because they became ill with cotrimoxazole-resistant PCP.

Given how limited our options currently are for caring for HIV-infected African children and given the stakes involved, it is evident that a carefully designed prospective study—either a cohort study or a randomized placebo trial—must be conducted before health policy decisions can be made with much confidence.

Christopher J. Gill, Davidson Hamer, and Donald M. Thea
Center for International Health and Development, Boston University School of Public Health, Boston, Massachusetts

Reference

Figure 1. Population structure of Pneumocystis carinii pneumonia (PCP) among African children as a function of cotrimoxazole prophylaxis. The total number of children is represented as A + B; the total number of children with PCP is represented as a + b. The ideal measure of risk, by cotrimoxazole use, of developing PCP is represented as (a/A)/(b/B). The actual measure of risk of developing PCP used in Madhi et al. [1] is represented as (a/c)/(b/d). Shaded boxes represent population proportions that cannot be estimated given data available to the researchers. CTM, cotrimoxazole; PCP, Pneumocystis carinii pneumonia.
has been successful in preventing PCP among HIV-1–infected children in developed countries, where the burden of pediatric HIV-1 infection has fortunately remained a small fraction of that currently experienced in sub-Saharan African countries [4]. It is unfortunate, however, that—aside from all-encompassing recommendations by the Joint United Nations Programme on HIV/AIDS and the World Health Organisation for the provision of TMP-SMX prophylaxis to HIV-1–infected children [5]—little consideration has been given to the practical implementation of widespread TMP-SMX prophylaxis in heavily-burdened sub-Saharan African countries that have limited health care resources. We concur with Gill et al. [1] that, despite the success of TMP-SMX prophylaxis in developed countries and in developing countries such as Thailand [4,6], a prospective study is warranted in sub-Saharan African countries to define, not only the effectiveness of TMP-SMX prophylaxis amongst HIV-1–infected children, but also the best method of its provision in resource-poor countries.

**References**


**Role of Antibody in Recovery from Severe Vaccinia Virus Infection**

Str.—The excellent review by Bray and Wright states that recovery from vaccinia virus infection occurs “through the development of a cell-mediated immune response” and that “by the mid-1960s, it had become clear that progressive vaccinia resulted from defective cellular immune function” [1, p. 772, p. 768]. I disagree and suggest that the available evidence from animal models and human studies suggests that humoral, as well as cellular, immunity has an important role in recovery from this viral infection. The opinion that developed or solidified in the 1960s was based on the belief that patients with severe vaccinia virus infections had isolated defects in cell-mediated immunity [2].

Patients with progressive vaccinia rarely have defects only in cellular immunity. Essentially all of the adults described in the comprehensive review by Bray and Wright had diseases affecting both antibody formation and cellular mechanisms (table 3 in [1]). Sixteen of these 33 adults had chronic lymphocytic leukemia, a disease that interferes with antibody formation.