Figure 1 (facing page). Effects of Statins on T-Cell Activation.

Panel A shows Jurkat T cells that were incubated with 10 μM atorvastatin or medium. The cells were then fixed with 4 percent paraformaldehyde and incubated with cholera toxin B, labeled with phycoerythrin. Cholera toxin B binds to glycosphingolipid GM1, which is a marker for lipid-raft domains. T cells exposed to atorvastatin show alterations in the expression and distribution of lipid-raft domains. In Panel B, the T-cell receptor (TCR) and costimulatory molecules, including lymphocyte function–associated antigen 1 (LFA-1), CD28, CD4, and CD40 ligand (CD40L), are recruited to lipid rafts after activation. Statins interfere with the activation of T cells by depleting membrane cholesterol and disrupting the integrity of lipid rafts. Statin treatment causes the exclusion from lipid microdomains of raft-associated molecules such as the Lck protein tyrosine kinase, the inhibition of actin polymerization, and the formation of a stable immunologic synapse and therefore disrupts T-cell activation.

evidence suggest that the inhibition of cholesterol synthesis by statins disrupts these lipid rafts and thereby influences the function of lymphocytes (Fig. 1).

Could all the immunomodulation by statins be ascribed to their ability to reduce cholesterol levels in the cell membrane? Serum and membrane cholesterol may be differentially affected by statin treatment, and only by assaying both could the full effects of statins be identified. Although the changes in membrane cholesterol levels may be relevant only at sites of lymphocyte activation, as in atheroma or autoimmune diseases, the possibility that lymphocyte function may be generally impaired in the many patients who are taking statins raises a note of caution. However, even in the area of infection, there are suggestions that statin therapy has a favorable effect on sepsis and can reduce the replication of the human immunodeficiency virus.[6]

The notion that the antiinflammatory effects of statins ameliorate cardiovascular disease suggests that it should be possible to create other antiinflammatory agents, perhaps tailored to the specific immunologic abnormalities in atheroma. Determining the mechanisms of action of statins and their relative importance will help to rationalize the design of such therapies.

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Bacterial Infections — A Major Cause of Death among Children in Africa

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For the past 25 years, since the United Nations Children's Fund (UNICEF) has been publishing estimates of mortality among children worldwide, the international medical community has been aware of the appalling burden of early deaths among African children. Early studies indicated that, in the absence of any effective medical care, children born in a rural African village had a probability of death before the age of five years of 30 to 50 percent.[1] From the outset, it was understood that many of these deaths result from the combined effect of poverty and malnutrition.[2] Since 1980, mortality rates have fallen but remain high by global standards. Twelve African countries still report official death rates for children under the age of five of more than 20 percent. Community-based studies of death among children have been able to attribute these deaths to a number of common causes, either syndromes or specific diseases (Table 1).

These studies have suggested that the most important cause of death among children in Africa is malaria. The studies are based on the administration of a questionnaire in an interview with the family, conducted after the child's death, usually by a health

Table 1. Official Estimates of Mortality among Children under 5 Years of Age According to Cause in Sub-Saharan Africa and Globally in 2002.*

Cause of Death	Africa	Global
	percent	
Acute respiratory infection	16	18
Diarrheal disease	14	15
Malaria	22	10
Measles	8	5
HIV or AIDS	8	4
Neonatal deaths	13	23
Other causes	19	25
	number	
All causes	4.5 million	10.9 million

* Data are from the World Health Organization (WHO)[3] and reflect the WHO African region, which excludes most North African countries, Somalia, and Sudan. Many of the deaths that were classified as due to "other causes" may actually belong among the main causes listed. A total of 54 percent of all deaths among children are believed to be associated with malnutrition. HIV denotes human immunodeficiency virus, and AIDS the acquired immunodeficiency syndrome.

worker in the home. The findings are then interpreted by a physician. Children who have died as a result of a short illness associated with fever are generally regarded as having died from malaria. Coexisting malnutrition is not considered in these studies. In recent years, community-based studies of the incidence of invasive bacterial disease caused by *Haemophilus influenzae* type b or *Streptococcus pneumoniae* have been undertaken as part of an attempt to determine the probable effect of vaccines against those organisms. Most identified cases were manifested as either pneumonia or meningitis and as such did not alter perceptions regarding the overall burden of morbidity and mortality attributable to bacterial infections.

The study by Berkley et al.[4] in this issue of the *Journal* breaks new ground in that it is a population-based evaluation of the incidence of all invasive bacterial disease in children living in a rural African community. The results are both surprising and enlightening. The incidence of invasive disease due to *H. influenzae* type b and pneumococcus is similar to that found in other population-based studies from sub-Saharan Africa. However, this study also presents data on the incidence of other bacterial infections, all of which are associated with a substantial and similar risk of death. The annual overall risk of any bacteremic disease for children was 505 per 100,000 children under the age of five years, a risk that is equivalent to a 2.5 percent probability of a child's acquiring invasive bacterial infection during the first five years of life. This figure is much higher than is the risk of invasive bacterial infection among U.S. children, and the outcome is much worse. Since many children in the study area became ill and died without medical care, this number must represent a substantial underestimation of the true incidence.

In the study, 28 percent of children admitted to the hospital with bacteremia died. Even more important, 26 percent (308 of 1184) of hospital deaths were associated with bacteremia. This finding compares with 22 percent of the deaths that were associated with malaria, suggesting that bacterial disease may be responsible for more deaths in children than malaria in this area where malaria is endemic. Is this an accurate indication of mortality patterns in the community, given that most deaths of children occur in the home? Did the children who died at home die from a spectrum of causes similar to that among children who died after reaching the hospital? Both malaria and bacterial illness are amenable to relatively simple therapeutic approaches, but antimalarial drugs tend to be more widely available in African communities than are antibiotics. Therefore, in a rural community, bacteremia may be even more important as a cause of death among children than it is in a hospital setting, since the management of bacteremic illness in the community is likely to be less effective than the management of malaria.

The analysis presented by Berkley et al. focuses on the role of the human immunodeficiency virus (HIV) and malnutrition as cofactors in bacteremic childhood illness. The prevalence of HIV infection among pregnant women in the study area was around 10 percent, which tragically is about average for sub-Saharan Africa. Both HIV infection and malnutrition were associated with an increased risk of bacteremia among children admitted to the hospital, but only 18 percent of children admitted with bacteremic illness were infected with HIV, whereas severe malnutrition was present in 37 percent, suggesting that the latter is a more important cofactor.

During the past six years, the world of international health care has been dominated by high-profile efforts to control HIV infection, malaria, and tuberculosis. Of these, malaria is seen as the most important contributor to death among children in

Africa. This study gives us cause to question whether this very narrow, disease-based approach is indeed appropriate and whether the most important causes of death among children have been appropriately targeted. Even in an area of rural Kenya with high rates of HIV infection and malaria, there appear to be more deaths of children associated with bacterial infection than with malaria, with malnutrition still the main cofactor. Global health strategies, like any other public health activities, should be based on evidence. This study has highlighted just how weak is our understanding of the causes of death among children in Africa.

Control of the problem of bacterial infections is complex. Vaccines against *H. influenzae* type b have already been introduced in a number of African countries, including Kenya, with the assistance of the Global Alliance for Vaccines and Immunization. Sadly, there is now concern about the sustainability of those programs, although the study by Berkley et al. provides further evidence of the importance of *H. influenzae* type b in African children and, for the first time, gives an indication of the effect of this pathogen on mortality. The currently available pneumococcal conjugate vaccine is very expensive and covers a limited range of serotypes, yet this approach may have an important role in the prevention of pneumococcal disease in the future, probably in combination with the 23-valent pneumococcal polysaccharide vaccine. In the study by Berkley et al., more than 70 percent of pneumococcal isolates in children who were old enough to have been vaccinated were of serotypes that are included in the nine-valent conjugate vaccine, which has undergone trials in South Africa and the Gambia. A much lower proportion of isolates would be included in the commercially available seven-valent vaccine, which lacks the dominant serotype 1, which was responsible for 24 percent of isolates in the study.

For the remaining causes, there are no vaccines available at present. Thus, prevention of deaths from these conditions rests with improvement in the living conditions of children, reduction in the high rates of malnutrition, improved recognition of illness requiring medical care, and more prompt treatment with antibiotics and lifesaving supportive measures such as oxygen and fluids. Evidence that prompt treatment is necessary was found in the high proportion of deaths associated with bacteremia that occurred in children who were newly admitted to the hospital. Presumably, if such children had been identified and treated earlier, many of the deaths might have been averted.

There is no substitute for the provision of an adequate and accessible health care system that can deal with the treatable causes of death in children, such as bacterial infection. There are no shortcuts. Under the Convention on the Rights of the Child, countries are now obliged to provide adequate health services for their children. Such services must be comprehensive, integrated, and accessible to all. The lack of functional, basic health services stands as a major barrier to resolving the global tragedy of mortality among children, particularly in sub-Saharan Africa.[5]

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