and effectiveness with active surveillance if this vaccine is deployed.

What does this vaccine mean for the future of the control and elimination of malaria? The considerable increase in global funding is paying dividends. In places where effective interventions (insecticide-treated bed nets, insecticides, and artemisinin-combination treatments) are being intensively deployed, malaria morbidity and mortality are falling. Several new, simple, affordable interventions, such as seasonal chemoprevention among young children in areas of seasonally high malaria transmission and the use of artesunate in patients with severe malaria, can also provide substantial reductions in mortality. The very low rate of death from malaria in this large trial (only 10 deaths directly attributed to malaria) testifies to the benefits of providing early diagnosis and effective antimalarial treatment. But there are real dangers ahead. How will the necessary funding be sustained in the face of a global economic downturn, along with a reduction in political pressure associated with declining mortality from malaria? In addition, artemisinin resistance in malaria parasites and pyrethroid resistance in anopheline mosquito vectors pose very serious threats.

All the investigators who have labored long and hard in the development and evaluation of this malaria vaccine deserve congratulations. It is a great achievement and an important advance, but they know that this partially protective vaccine is not the sole solution to the control and elimination of malaria. After registration, the definitive WHO guidance, expected in 2015, may recommend that the inclusion of RTS,S/AS01 in the multipronged attack against malaria is justified. The key question of how long the protection against malaria lasts, particularly in the anticipated context of declining malaria transmission, remains open. An assessment of an 18-month booster dose will not be available until 2014. Another key issue is whether efficacy varies according to the intensity of transmission. We also do not know yet how much the vaccine will cost. All these factors are essential components of the objective assessments of cost-effectiveness that should form the basis of future global and national policy decisions.

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1. Malaria: initiative for vaccine research (IVR). Geneva: World Health Organization (http://www.who.int/vaccine_research/Malaria/en/index.html).
2. The RTS,S Clinical Trials Partnership. First results of phase 3 trial of RTS,S/AS01 malaria vaccine in African children. N Engl J Med 2011;365:1863-75.
3. Bejon P, Lusingu J, Olotu A, et al. Efficacy of RTS,S/AS01E vaccine against malaria in children 5 to 17 months of age. N Engl J Med 2008;359:2521-32.
4. Asante KP, Abdulla S, Agnandji S, et al. Safety and efficacy of the RTS,S/AS01(E) candidate malaria vaccine given with expanded-programme-on-immunisation vaccines: 19 month follow-up of a randomised, open-label, phase 2 trial. Lancet Infect Dis 2011; 11:741-9.
5. Olotu A, Lusingu J, Leach A, et al. Efficacy of RTS,S/AS01E malaria vaccine and exploratory analysis on anti-circumsporozoite antibody titres and protection in children aged 5-17 months in Kenya and Tanzania: a randomised controlled trial. Lancet Infect Dis 2011;11:102-9.

Childhood Obesity and Coronary Heart Disease

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Obesity is the most common nutritional problem among children in both developed and underdeveloped countries. Despite efforts over the past decade to prevent and control obesity, data from the 2003–2006 National Health and Nutrition Examination Surveys (NHANES) show that 16.3% of children and adolescents, 2 to 19 years of age, are obese (i.e., have a body-mass index [BMI] above the 95th percentile for age and sex).[1]

There is strong epidemiologic evidence that obesity in childhood is associated with an increased incidence of atherosclerosis in adulthood. Postmortem studies have shown that obesity in childhood and adolescence is associated with increased evidence of atherosclerosis at autopsy, especially in males.[2] Epidemiologic studies involving children have documented a strong association between the major known atherosclerosis risk factors (elevated blood pressure, dyslipidemia, inflammatory markers, and insulin resistance) and childhood obesity.[3] Baker et al.,[4] using data on childhood BMI z scores and information from

the Danish National Cause of Death Register, found that, with each one-unit increase in BMI z score at 7 to 13 years of age in the case of boys and at 10 to 13 years of age in the case of girls, there was a significant increase in the risk of a coronary event during adulthood. Bibbins-Domingo and colleagues[5] used data on the prevalence of overweight among adolescents in the 2000 NHANES to estimate the likely prevalence of obesity among 35-year-old persons in 2020. They then used this estimate in a computer-simulation model of coronary heart disease to predict the likely annual excess incidence and prevalence of coronary heart disease attributable to obesity from 2020 to 2035. Their model predicted that, by 2035, the prevalence of coronary heart disease in adults will increase by 5 to 16% and that more than 100,000 excess cases of coronary heart disease will be directly attributable to childhood obesity.[5]

Despite the overwhelming evidence linking childhood obesity to adult atherosclerotic heart disease, there is also evidence that obesity in childhood does not guarantee that cardiovascular risk will be increased in adulthood. We have previously shown that among obese adolescents, an improvement in weight status and a decrease in body fatness is associated, at least in the short term (20 weeks), with a decrease in systolic and diastolic blood pressure; a decrease in total cholesterol, low-density lipoprotein cholesterol, and triglyceride levels; an increase in high-density lipoprotein cholesterol levels; and a decrease in insulin resistance.[6,7] The article by Juonala and colleagues[8] in this issue of the *Journal* adds considerably to our observations by providing long-term follow-up data that suggest that cardiovascular risk in adulthood is reduced if obesity is treated or prevented in childhood. In their study of 6328 subjects, those with persistently high adiposity status from childhood to adulthood had significantly increased risks of diabetes, hypertension, dyslipidemia, and carotid-artery atherosclerosis. In contrast, the risks of all these outcomes among overweight or obese children who became nonobese as adults did not differ significantly from the risks among those who were never obese.

The study by Juonala et al. has several limitations. It was observational (with no attempt made to prevent weight gain or to reduce weight), there were differences in the acquisition of data among the four cohorts, there was a lack of comprehensive serial data, and most of the study participants were white. However, taking into account data from studies of pediatric weight-loss interventions, which have documented that weight loss is associated with a reduction in cardiovascular risk factors,[6,7,9] I believe that the major finding in the study by Juonala et al. — that childhood obesity does not permanently increase cardiovascular risk provided that childhood obesity is successfully treated — is valid.

Given that atherosclerotic cardiovascular disease is a major driver of health care expenditures in the United States, the development of more effective strategies for treating and preventing childhood obesity is a cost-effective way of achieving a long-term reduction in atherosclerotic cardiovascular disease. To date, most studies of interventions to prevent childhood obesity have been school-based or community-based, and although these interventions are effective in modifying the diet and exercise habits of children, they unfortunately have limited value in preventing the long-term development of overweight and obesity.[10] Juonala et al. found that, over an interval of almost 25 years, only 15% of subjects who were of normal weight as children were obese as adults, whereas 65% of those who were overweight or obese as children and 82% of those who were obese as children were obese as adults. These figures suggest that targeting interventions for obesity prevention and treatment specifically to children who are at high risk for becoming obese will prove to be a more valuable and more cost-effective strategy than targeting these interventions to whole populations of children. If we want to reduce the incidence of adult heart disease and thereby start to control the continuing escalation in U.S. health care expenditures, now is the time to do whatever it takes to develop more effective methods for both the prevention and the treatment of childhood obesity.

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1. Ogden CL, Carroll MD, Flegal KM. High body mass index for age among US children and adolescents, 2003-2006. JAMA 2008; 299:2401-5.
2. Strong JP, Malcom GT, McMahan CA, et al. Prevalence and extent of atherosclerosis in adolescents and young adults: implications for prevention from the Pathobiological Determinants of Atherosclerosis in Youth Study. JAMA 1999;281:727-35.
3. Juonala M, Järvisalo MJ, Mäki-Torkko N, Kähönen M, Viikari

JS, Raitakari OT. Risk factors identified in childhood and decreased carotid artery elasticity in adulthood: the Cardiovascular Risk in Young Finns Study. Circulation 2005;112:1486-93.
4. Baker JL, Olsen LW, Sørensen TI. Childhood body-mass index and the risk of coronary heart disease in adulthood. N Engl J Med 2007;357:2329-37.
5. Bibbins-Domingo K, Coxson P, Pletcher MJ, Lightwood J, Goldman L. Adolescent overweight and future adult coronary heart disease. N Engl J Med 2007;357:2371-9.
6. Rocchini AP, Katch V, Schork A, Kelch RP. Insulin and blood pressure during weight loss in obese adolescents. Hypertension 1987;10:267-73.
7. Becque MD, Katch VL, Rocchini AP, Marks CR, Moorehead C. Coronary risk incidence of obese adolescents: reduction by exercise plus diet intervention. Pediatrics 1988;81:605-12.
8. Juonala M, Magnussen CG, Berenson GS, et al. Childhood adiposity, adult adiposity, and cardiovascular risk factors. N Engl J Med 2011;365:1876-85.
9. Meyer AA, Kundt G, Lenschow U, Schuff-Werner P, Kienast W. Improvement of early vascular changes and cardiovascular risk factors in obese children after a six-month exercise program. J Am Coll Cardiol 2006;48:1865-70.
10. Flodmark CE, Marcus C, Britton M. Interventions to prevent obesity in children and adolescents: a systematic literature review. Int J Obes (Lond) 2006;30:579-89.

Toward Better Treatment for Lupus Nephritis

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Systemic lupus erythematosus is a prototypical autoimmune disease that can potentially involve every organ. Its clinical spectrum is therefore extremely heterogeneous and varies from relatively mild cases (e.g., involving only the skin or joints) to life-threatening manifestations, with renal impairment, severe cytopenias, or central nervous system disease, not to mention an increased rate of thromboembolic events.[1]

Kidney involvement (mainly glomerulonephritis) occurs in at least one third of patients with lupus and significantly affects survival.[2] The initial clinical presentation of lupus nephritis ranges from asymptomatic proteinuria discovered on routine urinalysis to the nephrotic syndrome with or without renal impairment. Histologic examination of a renal-biopsy specimen is a pivotal step in confirming the diagnosis and guiding therapy. Immunosuppressive therapy consists of glucocorticoids combined with a cytotoxic drug (which for decades has been high-dose intravenous cyclophosphamide) to achieve a prompt response. The high rate of renal relapse (35%) justifies long-term maintenance immunosuppression. Between 10 and 20% of patients with lupus nephritis ultimately require renal-replacement therapy.

Within the past decade, clinical researchers — thanks to the outstanding collaboration of patients with lupus nephritis — have carried out well-conducted, controlled trials aimed at improving the efficacy and safety of the immunosuppressive regimen. Although the jury is still out on several issues, advances have been achieved, such as the use of a more patient-friendly, short-course induction regimen, in which low-dose intravenous cyclophosphamide is followed by long-term azathioprine maintenance therapy (as described in the Euro-Lupus Nephritis Trial[3]), and the introduction of mycophenolate mofetil, an immunosuppressive drug used successfully in transplantation. Mycophenolate mofetil was shown to be at least equivalent to cyclophosphamide in inducing an initial renal response,[4-6] thereby earning it a place in the armamentarium for the treatment of lupus nephritis, although long-term data on patients who have undergone induction therapy with mycophenolate mofetil are still eagerly awaited.

In this issue of the *Journal*, Dooley et al.[7] report the results of the maintenance phase of the Aspreva Lupus Management Study (ALMS), which compared the efficacy and safety of azathioprine and mycophenolate mofetil as maintenance therapy for patients with lupus nephritis who had responded to induction therapy with either mycophenolate mofetil or intravenous cyclophosphamide. After 36 months, mycophenolate mofetil appeared to be superior to azathioprine with respect to time to treatment failure (a composite primary end point), time to renal flare, and time to rescue therapy, regardless of induction group. Withdrawals due to severe adverse events were significantly more common among the patients given azathioprine. Although the study was not powered for subset analyses, the differential effect between mycophenolate mofetil and azathioprine was more stringent in black patients. Of note, among patients given mycophenolate mofetil for maintenance, those who had previously received induction therapy with intravenous cyclophosphamide had fewer treat-