A trial of M72/AS01(E) vaccine to prevent tuberculosis

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THE AUTHORS REPLY: We completely agree with Wang and Yang that China has made exceptional strides toward elimination of schistosomiasis. As highlighted previously,[1] disease control through the use of praziquantel alone is unlikely to interrupt transmission. An integrated transdisciplinary strategy is essential. Given the zoonotic nature of *S. japonicum* in Asia, where both domestic animals and wildlife continue to transmit the parasite,[2] this strategy is particularly pertinent. Lessons learned from zoonotic control in China will become more critical in Africa as the 2030 WHO guidelines, with the goal of elimination, are announced. Furthermore, evidence is mounting regarding the risk of zoonotic transmission of both *S. mansoni* and, through hybridization with animal schistosomes, *S. haematobium*.[3,4] Indeed, the sustained high prevalence of schistosomiasis indicated by our data from West Africa may reflect this risk.

We focused on country programs facilitated by the Schistosomiasis Control Initiative, so our study was restricted to Africa and Yemen, and we followed the standard WHO treatment guidelines. Therefore, the inclusion of data from China was inappropriate. Nevertheless, schistosomiasis control and its interruption are global efforts in which shared expertise from each country is essential in order to tackle this debilitating disease.

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A Trial of M72/AS01$_E$ Vaccine to Prevent Tuberculosis

TO THE EDITOR: Tait et al. (Dec. 19 issue)[1] report that the M72/AS01$_E$ vaccine had an efficacy of 50% against pulmonary tuberculosis disease in a phase 2B trial after 3 years of follow-up, a result that represents the first tuberculosis vaccine in a century that has had significant efficacy. M72/AS01$_E$ was evaluated in three countries: South Africa, Kenya, and Zambia. In the vaccine group, 13 cases of tuberculosis occurred, and in the placebo group 26 cases occurred. An important note of caution, however, is that the number of persons tested — and consequently the number of cases counted — was highly uneven among countries: in the vaccine group, there were 11, 2,

and 0 cases in South Africa, Kenya, and Zambia, respectively; in the control group, the respective numbers of cases were 24, 1, and 1. This implies that the major part of the efficacy of M72/AS01$_E$ is based on data from a single population, with limited representation of both the global lineages of *Mycobacterium tuberculosis* and human diversity. It is therefore important to coordinate efforts and soon demonstrate the efficacy of M72/AS01$_E$ in genetically and environmentally diverse human populations in which different lineages of *M. tuberculosis* are represented (e.g., bacille Calmette–Guérin vaccination is less protective against *M. tuberculosis*-Beijing than against other strains[2]) and in which there may be prevalent coexisting medical conditions, including infection with the human immunodeficiency virus.

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No potential conflict of interest relevant to this letter was reported.

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THE AUTHORS REPLY: We agree with Ottenhoff's comments. Although we have evidence that the sequences from which the M72/AS01$_E$ candidate vaccine is derived are highly conserved among mycobacterium strains circulating worldwide and that the predicted putative T-cell epitopes in the vaccine cover a wide array of HLA alleles from European, U.S., Asian, and African populations,[1] we acknowledged in our article that there is a need to confirm these initial efficacy results in larger trials conducted over a longer period of time and in a broader range of populations. Persons who have negative results on the interferon-γ release assay, who represent a variety of ethnic backgrounds, who live in a wide range of geographic locations, and who represent a variety of age groups should be included in these trials.

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Baroreflex Dysfunction

TO THE EDITOR: The use of 24-hour ambulatory blood-pressure monitoring can be helpful in the diagnosis and management of baroreflex dysfunction. Although bedside monitoring of orthostatic blood pressure is useful in screening patients for dysfunction, as noted by Kauffman et al. (Jan. 9 issue),[1] the data it provides do not reflect the underlying complexity of hemodynamic profiles in these patients. Ambulatory blood-pressure monitoring provides data on blood-pressure variability, an independent predictor of cardiovascular events.[2] In one study involving patients with a positive autonomic reflex screen (a well-defined test of various autonomic domains), ambulatory blood-pressure monitoring detected reversal of circadian rhythm, postprandial hypotension, and nocturnal hypertension in 92.3%, 100%, and 100%, respectively.[3] In a trial in which ambulatory blood-pressure monitoring was used, the autonomic nervous system regulation index was also shown to have a significant relationship with blood pressure variability.[4] This approach also provided information on the magnitude of postprandial declines in systolic blood pressure that correlated with severity of silent cerebrovascular damage.[5] Postprandial hypotension is associated with a risk of autonomic dysfunction that is five times as high as that among persons