Schistosomiasis is a debilitating neglected tropical disease caused by infection with parasitic trematodes of the genus *Schistosoma*. Six species of *Schistosoma* are the basis of clinical disease in humans, altogether responsible for over 290,000 deaths annually.1 The clinical manifestations of schistosomiasis are chronic and insidious, including fever, anemia, growth retardation, genital lesions, hepatosplenomegaly and irreversible organ damage.2 According to recent estimates, schistosomiasis is endemic in 78 countries with over 800 million people at risk for infection.3 Despite mass drug administration programs with praziquantel, the prevalence of schistosomiasis remains high. A vaccine is urgently needed to control transmission of this disease.4 Making a vaccine for a multicellular eukaryotic parasite whose genetic machinery is exactly similar to their host, requires more detailed understanding of both host as well as the parasites. An effective schistosome vaccine could offer sustainable reduction in both the prevalence and transmission of the disease.5, 6 The prominent Schistosomiasis vaccines include *S. haematobium* 28-kD Glutathione S-Transferase (rSh28GST), *S. mansoni* 14-kDA Fatty Acid Binding Protein (Sm14), *S. mansoni* Tetraspanin-2 (Sm-TSP-2) and *S. mansoni* Sm-p80/GLA-SE, which are at various stages of human clinical trials.7 In May 2022, Infectious Diseases Clinical Research Consortium (IDCRC) researchers started conducting a clinical trial of Sm-p80/GLA-SE (Schistoshield). The trial could help pave the way for the world’s first vaccine against the disease, offering a safe and cost-effective option to lower its prevalence worldwide.

Currently, adenovirus vectors are being tested as subunit vaccine systems for numerous infectious agents ranging from malaria to HIV to SARS-CoV-2. Several of the presently approved vaccines against SARS-Coronavirus-2 (AstraZeneca/Oxford University, Johnson & Johnson’s Janssen COVID-19 Vaccine, and Sputnik V) are based on adenovirus DNA vectors as carriers for the genetic information for the SARS-COV-2 spike glycoprotein.8 However, the negative aspect of adenoviruses is that it can get integrated into human genome as provirus and lead to serious and even fatal infections such as pneumonia or meningioencephalitis, especially in immunocompromised individuals and children.9 In a recent issue of *eBiomedicine*, Perera DJ et al.8 investigated the performance of a low dose adenovirus vectored vaccine expressing *Schistosoma mansoni* Cathepsin B, to find out if this new putative heterologous prime and boost vaccine with recombinant protein can protect experimental host from infection with schistosomiasis in a murine model. *S. mansoni* Cathepsin B (SmCB) is a parasitic gut peptidase necessary for helminth growth and maturation are essential for the establishment and survival of *Schistosoma mansoni*. This blood fluke expresses a number of gut-associated peptidases that degrade host blood proteins, including hemoglobin, as a means of nutrition.9 Perera DJ et al.8 constructed an adenovirus serotype 5 containing *S. mansoni* Cathepsin B (AdSmCB) and delivered it intramuscularly in a heterologous prime and boost vaccine with recombinant protein. The study on AdSmCB vaccine although preliminary in nature, elicited a high T cell cytokine expression and higher protective capacity at very low dose which could preferably avoid the adenovirus vaccine related adverse effects. Higher systemic and cell mediated immune responses, consisting of IgG2c, Th1 effectors, and polyfunctional CD4+ T cells, were detected after the administration of heterologous AdSmCB. The SmCB increased T cell IFNγ production and promoted CD4+ T cell polyfunctionality which was determined by elevated levels of RANTES, a T cell associated chemokine responsible for IFNγ production. Although more of a Th1 favored immune response was elicited, the Th2 response provided by SmCB protein boosts were maintained. This balanced Th1/Th2 immune response in the current findings resulted in a significant protection of experimental mice from *S. mansoni* infection, which are similar to other vaccine formulations that are already in clinical trials.

In a nutshell, this investigation describes a viral vectored vaccine which prophylactically protects from schistosomiasis, at levels comparable to others in pre-
clinical work and those currently in clinical trials, through a platform which has been widely used in humans and can be easily scaled up for global production. This adenovirus vectored vaccine elicits strong humoral immunity and cellular effectors, balancing Th2 and Th1 arms of immunity to target SmCB-expressing in larvae and adult worms. Additionally, parasite burden reduction by this vaccine led to prevention of pathology caused by S. mansoni egg deposition, which is crucial to alleviating chronic morbidities and may significantly aid regions where coinfestations make liver pathologies lethal. The main drawback of this study is that it is DNA based and such a vaccine proved to be inefficacious as demonstrated by considerable number of breakthrough infections when used against SARS-CoV-2 or even leading to the death of the vaccinated individuals.

While we strongly support this investigation, in order for the adenovirus vectored SmCB to enter the first phase of human clinical trial, AdSmCB still has to go a long way. Firstly, all the components of this new vaccine need to be tested for their endotoxin levels. During preclinical development of the next generation vaccines, endotoxin levels should be closely monitored despite the heterogeneity in licensed vaccines. Routine measurement of endotoxin levels is necessary to properly understand preclinical animal study results. The endotoxin levels should also be closely monitored due to the potential of a synergistic effects. A level of <20 EU/mL for recombinant subunit vaccine types is recommended.10 Secondly, once the authors produce the adenovirus vectored vaccine expressing Schistosoma mansoni egg deposition, which is crucial to alleviating chronic morbidities and may significantly aid regions where coinfestations make liver pathologies lethal. The main drawback of this study is that it is DNA based and such a vaccine proved to be inefficacious as demonstrated by considerable number of breakthrough infections when used against SARS-CoV-2 or even leading to the death of the vaccinated individuals.

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Contributors
Gul Ahmad wrote and revised this commentary.

Declaration of interests
The author has no conflicts of interest to disclose.

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