



**Universiteit
Leiden**
The Netherlands

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

Ottenhoff, T.H.M.

Citation

Ottenhoff, T. H. M. (2020). A trial of M72/AS01(E) vaccine to prevent tuberculosis, 382(16), 1576-1577. doi:10.1056/NEJMc2001364

Version: Publisher's Version

License: [Licensed under Article 25fa Copyright Act/Law \(Amendment Taverne\)](#)

Downloaded from: <https://hdl.handle.net/1887/3181109>

Note: To cite this publication please use the final published version (if applicable).

Wei Wang, M.Sc.
Kun Yang, Ph.D.

Jiangsu Institute of Parasitic Diseases
Wuxi, China
yangkun@jipd.com

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

1. Deol AK, Fleming FM, Calvo-Urbano B, et al. Schistosomiasis — assessing progress toward the 2020 and 2025 global goals. *N Engl J Med* 2019;381:2519-28.
2. Xu J, Steinman P, Maybe D, et al. Evolution of the national schistosomiasis control programmes in the People's Republic of China. *Adv Parasitol* 2016;92:1-38.
3. Ross AG, Chau TN, Inobaya MT, Olveda RM, Li Y, Harn DA. A new global strategy for the elimination of schistosomiasis. *Int J Infect Dis* 2017;54:130-7.
4. Yang K, Yang HT, Liang YS, et al. A path analysis on China's participation in global health governance: a case study of China Aid of Schistosomiasis Control in Zanzibar. *Zhongguo Xue Xi Chong Bing Fang Zhi Za Zhi* 2019;31:14-8. (In Chinese.)
5. Wang XY, He J, Juma S, et al. Efficacy of China-made praziquantel for treatment of Schistosomiasis haematobium in Africa: a randomized controlled trial. *PLoS Negl Trop Dis* 2019;13(4): e0007238.

DOI: 10.1056/NEJMc2002117

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.

Arminder K. Deol, Ph.D.

London School of Hygiene and Tropical Medicine
London, United Kingdom
arminder.deol@lshtm.ac.uk

Michael D. French, Ph.D.

RTI International
Washington, DC

Joanne P. Webster, Ph.D.

Royal Veterinary College
London, United Kingdom

Since publication of their article, the authors report no further potential conflict of interest.

1. McManus DP. Defeating schistosomiasis. *N Engl J Med* 2019;381:2567-8.
2. Rudge JW, Webster JP, Lu D-B, Wang T-P, Fang GR, Basáñez MG. Identifying host species driving transmission of schistosomiasis japonica, a multihost parasite system, in China. *Proc Natl Acad Sci U S A* 2013;110:11457-62.
3. Catalano S, Sène M, Diouf ND, et al. Rodents as natural hosts of zoonotic schistosoma species and hybrids: an epidemiological and evolutionary perspective from West Africa. *J Infect Dis* 2018;218:429-33.
4. Webster BL, Diaw OT, Seye MM, Webster JP, Rollinson D. Introgressive hybridization of *Schistosoma haematobium* group species in Senegal: species barrier break down between ruminant and human schistosomes. *PLoS Negl Trop Dis* 2013;7(4): e2110.

DOI: 10.1056/NEJMc2002117

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 strains²) and in which there may be prevalent co-existing medical conditions, including infection with the human immunodeficiency virus.

Tom H.M. Ottenhoff, M.D., Ph.D.

Leiden University Medical Center
Leiden, the Netherlands
t.h.m.ottenhoff@lumc.nl

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

1. Tait DR, Hatherill M, Van Der Meeren O, et al. Final analysis of a trial of M72/AS01_E vaccine to prevent tuberculosis. *N Engl J Med* 2019;381:2429-39.

2. Verrall AJ, Chaidir L, Ruesen C, et al. Lower BCG protection against mycobacterium tuberculosis infection after exposure to Beijing strains. *Am J Respir Crit Care Med* 2020 Jan 8 (Epub ahead of print).

DOI: 10.1056/NEJMc2001364

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.

Dereck R. Tait, M.B., Ch.B

IAVI
Cape Town, South Africa

Olivier Van Der Meeren, M.D.

GlaxoSmithKline
Wavre, Belgium
olivier.x.van-der-meeren@gsk.com

Mark Hatherill, M.D.

South African Tuberculosis Vaccine Initiative
Cape Town, South Africa

Since publication of their article, the authors report no further potential conflict of interest.

1. Mortier MC, Jongert E, Mettens P, Ruelle JL. Sequence conservation analysis and in silico human leukocyte antigen-peptide binding predictions for the Mtb72F and M72 tuberculosis candidate vaccine antigens. *BMC Immunol* 2015;16:63.

DOI: 10.1056/NEJMc2001364

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