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The case for vaccine development in the strategy to eradicate river blindness (onchocerciasis) from Africa

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Onchocerciasis or river blindness is a neglected parasitic disease causing severe dermatitis and visual impairment, predominantly in Africa. Historically, onchocerciasis control targeted vector breeding sites, but the current strategy relies on mass administration of a single drug, ivermectin. As programmatic goals shift from reducing public health impact to active elimination, sole reliance on ivermectin is threatened by contraindications in areas coendemic for loiasis, an inability to break transmission in some foci, and the emergence of drug resistance. Here, we argue that prophylactic and therapeutic vaccines would accelerate elimination efforts and safeguard the enormous strides made in onchocerciasis control. These vaccines could be based on one or more of three lead candidates identified by a newly formed transatlantic partnership, The Onchocerciasis Vaccine for Africa Initiative.

Onchocerciasis is one of the most devastating of the neglected tropical diseases, and the target of some of the longest-running public health interventions ever waged in the history of tropical medicine. This disease, caused by the filarial nematode *Onchocerca volvulus*, is responsible for severe itching and depigmentation of the skin, as well as profound impairment of visual acuity, often leading to irreversible blindness. The colloquial name of 'river blindness' stems from the habits of the blackfly vector (*Simulium* spp.), which breeds exclusively in fast-flowing freshwaters. Approximately 30 million people (almost exclusively in Africa) are infected with *O. volvulus* [1]; with > 4 million experiencing severe itching, 746,000 with low vision, and 265,000 rendered blind [2]. All of the disease symptoms of onchocerciasis are caused by the first-stage larvae or microfilariae. These accumulate in the skin and migrate into the eyes in heavy infections (inflammatory reactions to dead microfilariae that drive pathology in both of these organs), whereas the adult worms reside in collagenous, subcutaneous nodules. The female worm releases approximately 1000 microfilariae per day and has a reproductive lifespan that can exceed 10 years.

Onchocerciasis is a scourge that continues to impose a global health burden of 0.5 million disability-adjusted life-years [1] and has long been the focus of efforts to alleviate morbidity and lost productivity. Although onchocerciasis was eliminated from several eastern and central African foci in the 1940s by spraying watercourses with DDT [3], the first concerted effort at large-scale, regional elimination of onchocerciasis began 41 years ago with the launch of the Onchocerciasis Control Programme (OCP) in West Africa. This was spearheaded by the then World Bank president, Robert McNamara, following an estimate that the disease was causing annual economic losses of US$ 30 million to the region [3]. Initially, the sole strategy of OCP was targeting of *Simulium* breeding sites by aerial spraying of an organophosphate larvicide. Subsequently, after it became clear that the veterinary anthelminthic, Mectizan (ivermectin), was effective against *O. volvulus* microfilariae, it was donated

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in 1987 by Merck & Co. for as long as needed to control the disease and increasingly became the lynchpin of OCP's activities. With the close of OCP in 2002, it was rightly celebrated that 40 million people in 11 countries were free of infection and 600,000 cases of blindness had been prevented, whereas 25 million hectares of abandoned arable land in fertile river valleys had been reclaimed for agricultural production [2]. However, with the launch of the new African Programme for Onchocerciasis Control (APOC) in 1995, efforts had already shifted from West Africa to 19 additional countries in the eastern and central regions of the continent. Annual community-directed treatment with ivermectin took center stage as the flagship of APOC. In parallel, the Onchocerciasis Elimination Program for the Americas tackled the much more limited disease burden in Latin America with semi-annual ivermectin treatment at consistently high rates of coverage, such that to date, transmission has been interrupted or certified as eliminated in 11 of 13 foci [4].

The critical question for onchocerciasis control since the close of OCP has been whether it is possible to eliminate the infection from Africa using mass drug administration alone. Until recently, the fundamentally different nature of the epidemiology of onchocerciasis between Latin America and Africa, including the geographical scale of endemic zones, greater vector competence and the logistics of maintaining high treatment coverage, was considered major barriers to elimination [5]. However, with the publication of a landmark study reporting abrogation of seasonal transmission in Mali and Senegal following 15–17 years of ivermectin treatment without vector control [6], a new goal of elimination was announced by APOC [7]. In 2012, the WHO estimated that 23 of 31 endemic African countries (including 11 ex-OCP countries) would have achieved elimination by 2020 [8], whereas the Mectizan Donation Program is committed to elimination of onchocerciasis 'where feasible' by 2025 [9]. In contrast, recent modeling projections indicate that eradication from Africa with ivermectin alone would not be completed until 2040 [10]. Indeed, in some endemic regions with perennial transmission, 10–18 years of annual ivermectin treatment have not broken the parasite lifecycle [11,12]. Furthermore, the fact that ivermectin can induce potentially fatal adverse events in individuals heavily coinfected with another filarial parasite, *Loa loa*, is a major barrier for onchocerciasis control in Central Africa, where 12 million people live in coendemic zones. Finally, the embryostatic effect of ivermectin on the female worm appears to be reduced in some repeatedly treated communities in Ghana and Cameroon [13,14], perhaps an early indicator of the emergence of resistance, as consistently observed in nematode parasites of animals. These considerations underscore the profound importance of continued investment in alternative control tools for onchocerciasis. The development of drugs targeting the adult worms (macrofilaricides) is one clear priority [15], but should not be an exclusive focus, as overcoming potential contraindications in young children and pregnant women may continue to be a major challenge. Thus, ivermectin is not administered to children under 5 years of age and a macrofilaricidal drug, doxycycline, cannot be given to children under 9 years. This renders children not only vulnerable to infection but also a reservoir for transmission to the rest of their community.

The ideal solution to accelerate and safeguard onchocerciasis elimination would be a vaccine, which could make a substantial impact in three, non-exclusive scenarios. First, a prophylactic vaccine to prevent the establishment of parasites in under-5s could be incorporated into pediatric immunization schedules (e.g., primary inoculation followed by two boosters) to protect this neglected segment of the population and reduce transmission to older cohorts. Second, immunoprophylaxis could be used in individuals of all ages in postelimination zones to protect communities from reinvasion events, such as infected black flies blown across operational boundaries by strong winds, or migration of infected itinerant workers. Third, a therapeutic vaccine for use in infected individuals could be a potent intervention tool for foci coendemic for loiasis, or where ivermectin alone has not broken transmission. Importantly, vaccination would form a part of an integrated control strategy that included existing chemotherapy, new or repurposed macrofilaricidal drugs, and where appropriate, vector control.

Considerable efforts in antigen discovery and vaccine candidate evaluation have already been made through the investments of the Edna McConnell Clark Foundation, the European Commission (Directorate-General for Research and Innovation) and the National Institute of Allergy and Infectious Diseases. When the Edna McConnell Clark Foundation river blindness program came to a close in 2000, eight recombinant antigens were field-tested in the most relevant animal model, *Onchocerca ochengi* in African cattle. Although no protection against adult worms was afforded, >40% of animals remained free of microfilariae [16]. Since this key experiment was completed, transatlantic research teams have converged on the selection of three antigens (RAL-2, 103 and mutated CPI-2) that consistently conferred high levels of protection in three animal models in three different laboratories using either recombinant protein or DNA immunization [17–19]. Of these, mutated CPI-2 is particularly noteworthy in that it can reverse the immunomodulation induced by the adult female worm, rendering microfilariae susceptible to protective immune mechanisms [17]. As such, it is a lead candidate for a therapeutic vaccine and could be bolstered in combination with other immunomodulatory targets mined from recent 'omic' analyses of filarial nematodes, including the public release of a reference-quality *O. volvulus* genome by the Wellcome Trust Sanger Institute [20].

This year, 13 academic institutions across Africa, Europe and the USA have joined together in a collaborative partnership, The Onchocerciasis Vaccine for Africa Initiative [21], the mission of which is to advance at least one vaccine candidate into Phase II human trials by 2020. This is an ambitious goal that will require a commensurate level of resources for the development and evaluation of optimal formulations, assessment of toxicity in preclinical screens and cGMP production and scale-up. Nevertheless, it is a critical priority for onchocerciasis control if the >$1 billion of funding for OCP and APOC is to be safeguarded and brought to

fruition by the elimination of onchocerciasis from Africa, and by implication, the global eradication of *O. volvulus*. We are still a long way from the 'last mile' of onchocerciasis elimination, even if the most optimistic forecasts are correct. When we do reach the endgame, we will want to be certain that we have the best possible tools to complete the audacious task set in motion by the launch of the OCP in 1974.

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