Meeting Report

Schistosomiasis Elimination Strategies and Potential Role of a Vaccine in Achieving Global Health Goals

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Abstract. In March 2013, the National Institute of Allergy and Infectious Diseases and the Bill and Melinda Gates Foundation co-sponsored a meeting entitled “Schistosomiasis Elimination Strategy and Potential Role of a Vaccine in Achieving Global Health Goals” to discuss the potential role of schistosomiasis vaccines and other tools in the context of schistosomiasis control and elimination strategies. It was concluded that although schistosomiasis elimination in some focal areas may be achievable through current mass drug administration programs, global control and elimination will face several significant scientific and operational challenges, and will require an integrated approach with other, additional interventions. These challenges include vector (snail) control; environmental modification; water, sanitation, and hygiene; and other future innovative tools such as vaccines. Defining a clear product development plan that reflects a vaccine strategy as complementary to the existing control programs to combat different forms of schistosomiasis will be important to develop a vaccine effectively.

INTRODUCTION

Schistosomiasis is a parasitic disease of tremendous global importance, with more than 240 million persons infected and at risk of severe morbidity and mortality. It is one of the major neglected tropical diseases (NTDs) within the National Institute of Allergy and Infectious Diseases global health agenda, and the Bill and Melinda Gates Foundation (BMGF) has also targeted achieving impact across multiple neglected infectious diseases, including schistosomiasis, through investment in strategy evaluation, product development, and operational research. The purpose of the meeting was to seek the schistosomiasis research community’s input on strategic initiatives and planning, and to strengthen collaborative research to explore novel approaches so as to maximize global impact on control and elimination. The meeting brought together a panel of global experts consisting of academic researchers, industry developers, government officials, and representatives from non-profit organizations and non-governmental organizations. The meeting participants reviewed the current schistosomiasis part in the goals and current strategies in the current World Health Organization (WHO) NTD Roadmap; evaluated gaps in tools to achieve an effective global elimination goal; addressed the potential role of vaccines and other interventions in achieving the global health goal; landscaped current schistosomiasis vaccine research and results; and identified unmet needs and opportunities for collaboration and synergy among ongoing programs, new and expanded mass drug administration programs, and vaccine research and development. The meeting also briefly discussed a desirable target product profile for schistosomiasis vaccines as a global health tool, and likelihood of technical success, and proposed a follow-up meeting to further develop a technology roadmap for schistosome vaccine research and development. Below is the summary of the collective views from the meeting participants.

SCHISTOSOMIASIS ELIMINATION APPROACH AND CHALLENGES

Approximately 85% of the 240 million schistosomiasis infections globally occur in sub-Saharan Africa. More than 800 million persons globally are at risk of infection. Estimates of the total disability-adjusted life years (DALYs) attributable to schistosomiasis vary widely; ranging from 3.3 million DALYs estimated in the 2010 Global Burden of Disease to as high as 36 million DALYs by Charles King in Acta Trop in 2010. The discrepancy in DALYs may be caused by subtle, differing, and difficult assessments of the types, outcomes, probabilities, and sequelae of various Schistosoma-associated disease morbidities, and misclassification of diseases associated with chronic schistosomiasis including malignancy. This discrepancy has led to difficulty in attributing losses in DALYs that are caused by infection-related conditions, such as anemia and growth stunting, because such conditions can have multiple possible causes in Schistosoma-endemic areas.

Current WHO treatment guidelines promote a strategy of control leading to elimination, focusing on treatment of school age children in a phased manner with different goals and tactics within each phase. Many of the WHO Strategic Plan milestones for schistosomiasis control have been reached in some targeted geographic areas. For example, in Egypt, an integrated mass drug administration (MDA) program between 1988 (when praziquantel [PZQ] was introduced) and 2010 was followed by a significant reduction in S. haematobium and S. mansoni prevalence and schistosomiasis-associated disease, especially bladder cancer, with no apparent evidence of emerging human PZQ resistance after widespread treatment (this decrease may not have been directly caused by MDA and may have been caused by other factors, including an overall decrease in Bulinus spp. populations). China presents as perhaps the most successful example of schistosomiasis...
control where the disease burden and transmission has been significantly reduced from 12 million cases to currently fewer than 500,000. Success in China may have been aided by seasonality because *S. japonicum* transmission only occurs five months per year versus year-round transmission in Africa, the Philippines, and other countries. With the recent commitment of Merck Serono to increase its annual donation of PZQ from 25 million to 250 million tablets and ongoing provision of the drug by other donors (including the Department for International Development, the U.S. Agency for International Development, and China), disease burden is anticipated to continue to decrease in the near future. To continue moving forward with the control and elimination program, in addition to the establishment of a global coordination mechanism for PZQ use, the development of national policies for preventative chemotherapy, and the adoption of a World Health Assembly resolution on schistosomiasis elimination, it will be vital to continue increasing treatment coverage and integration with MDA programs. Strong political and government commitment will be required to ensure control and elimination in most countries.

Despite the recognition that global control and elimination is possible, the inherent pathogenic features of the schistosome parasites present significant challenge. The symptoms associated with schistosomiasis are caused by host inflammatory immune responses and granuloma formation around eggs of the parasite that are retained in the host. The disease can be acute or chronic. Manifestations of chronic disease vary according to the infecting species and generally involve intestinal, hepatic, and urinary pathology, but schistosomiasis can also affect the central nervous system and other organs. The fact that many infected persons have low-intensity infections and are minimally symptomatic, however, adds to the difficulty of timely diagnosis, treatment, and transmission interruption. The different life cycles of *Schistosoma* spp. also necessitate specific elimination approaches for each of the parasite species. For example, effective control for *S. haematobium* seems more realistically feasible with the relatively short life span for the adult worm, the highly concentrated disease prevalence and infection intensity in school age children, and the easy and inexpensive diagnosis and treatment options for *S. haematobium*. In addition, massive multiplication of the schistosome parasites within snail intermediate hosts and continued exposure of persons to infection through household and domestic responsibilities present another layer of challenge, and may require new strategies and interventions to address the infection in the intermediate snail host or in domestic animal reservoirs (in the case of *S. japonicum*), as well as adult worm maturation in human hosts. The possibility of disease rebound after MDA termination was raised, and was reinforced by the examples from transmission hot spots, such as rural areas in the Philippines where prevalence has rebounded after incomplete MDA coverage. It is foreseeable that global elimination will be a significant challenge, and additional interventions will certainly be needed for an effective elimination toolbox.

Several existing tools potentially applicable to global elimination were discussed. For example, there has been strong political support and funding for water, sanitation, and hygiene (WASH) interventions as a strategy to reduce diarrheal disease and these programs have also proven to be effective as part of the integrated approach for schistosomiasis elimination in St. Lucia. As discussed at the meeting, the NTD community may need to leverage the existing WASH programs, strengthen the collaborative conversations between the two communities at all levels, and synergize efforts across multiple levels including strategic planning, mapping, and harmonization of educational messages. Snail control to interrupt transmission was also discussed as one of the existing components of an integrated control program. The important role of molluscicides in the past in reducing morbidity and the potential for biological control methods, such as the introduction of natural snail predators, in reducing transmission were also discussed. As part of the renewed efforts to highlight snail control, several key issues were discussed, including the need for providing training opportunities for local staff on snail identification and transmission, reducing costs of molluscicides, limiting ecologic disruption, developing new formulations and delivery systems, integrating snail control with vector control for other NTDs, implementing biological control strategies, and validating interruption of transmission. Although there was agreement that every effort should be made to advance the available tools for control and elimination, new tools such as vaccines were also advocated for development as a long-term strategy to ensure global sustainability.

**SCHISTOSOMIASIS MODELING AND PROJECTED IMPACT OF STRATEGIC APPROACH**

The meeting also included presentations of various mathematical and computational modeling studies that evaluated various program strategies involving multiple integrated tools and approaches. The impact of MDA has been studied in Kenya by using two working models: an equation-based model, representing six population strata, each with a different infection prevalence/intensity; and a Markov decision model with stratified worm burden, which incorporated population migration among communities. When existing WHO recommendations were used to guide treatment according to baseline prevalence, the models demonstrated that population coverage and frequency of treatment are important factors in achieving elimination. In addition, without reduction in transmission, infection prevalence will settle at a new lower prevalence equilibrium after treatment but will rebound over time. Such post-treatment rebound has also been observed in the field in the Philippines. Furthermore, treating high-prevalence communities alone is ineffective because of human migration patterns. Repeated treatment improves cure rates, reduces egg excretion, and will ultimately lead to elimination of heavy infection but not moderate or light infections. Preliminary modeling also predicts that targeted snail control (this approach has been more successful in Asia, perhaps because of the amphibious nature of the snails there) at optimal times can lead to better MDA outcomes, and deliberate reduction of transmission will be essential to achieve local elimination, especially in high-risk settings. Ultimately, full implementation of available strategies has considerable potential in reaching elimination. Finally, other modeling methodologies were also mentioned to better characterize transmission patterns using mapping data from the elimination programs in Liberia and Uganda.
A simplified deterministic model helped calculate the force of infection to serve as the basis for a future stochastic micro-simulation model. Such models will also be used to identify the threshold required to trigger remapping of community prevalence levels, to inform decision making for transition from MDA strategies to targeted control.

The impact of parasite vaccines on global elimination was extensively discussed. In the modeling for *S. japonicum* control using a pictorial model and assuming a certain level of efficacy, the frequency and coverage of treatment with PZQ clearly have a significant impact on lowering the prevalence and disease rebound rates; adding bovine treatment will further reduce the rebound rates. The *S. japonicum* modeling also supports the introduction of a vaccine to maximize treatment impact. For example, a regimen with three-time human treatment (80% coverage), one-time bovine treatment (90% coverage), and a vaccine (even with only 52% efficacy) would be sufficient to prevent disease rebound. Also, studies in the Poyang and Tongting lakes in China suggest that a cost-effective option is to treat just the small subgroup that carries the highest burden of infection. Large-scale treatment programs would be too expensive to sustain, particularly when human treatment has no long-lasting effect post-cessation. As such, combination strategies can be highly effective even if individual strategies are not optimal, especially when combining short-term treatment to decrease prevalence and long-term transmission blocking to decrease incidence. A hookworm modeling study illustrated the impact of different hookworm vaccines in the context of various ongoing MDA programs, integrating a compartmental transmission model with an operations model and Markovian clinical outcomes and economic model. The model showed that across different risk and disease burden levels, adding a hookworm vaccine (base case: 70% efficacy and five-year duration of protection) significantly lowered infection, disease, and cost burden when compared with MDA alone. As a result, adding a vaccine to MDA was a cost-effective measure (i.e., in most cases the incremental cost-effectiveness ratio was well below the threshold of three times the gross domestic product per capita). A similar approach will be applied to evaluate and guide the development and implementation of a schistosomiasis vaccine (e.g., the cost of a vaccine, the degree and duration of protection) and other interventions, as well as helping to prioritize data collection (e.g., morbidity, outcomes, and disability weight of schistosomiasis).

In summary, mathematical and computational modeling is an effective multi-modality tool to project the impact of schistosomiasis elimination efforts, guide intervention development and implementation, and prioritize data collection. Integrated modeling can assist program design needs and account for multiple integrated interventions, including MDA, WASH, snail control, and vaccine development and deployment. Furthermore, integrated modeling demonstrates potential investment impact and return on investment to various stakeholders. Although modeling is critical to designing elimination strategies, the panel members emphasized that better data regarding MDA, WASH, snail control, vaccine efficacy, epidemiology and parasitology, and health behaviors are needed. Modeling can help prioritize and quantify the value of these data needs. Another approach to address complicated modeling is to start modeling broadly and add more complexity later, such as cultural aspects of latrine use, human migratory patterns, seasonality of infection, vaccine regimen, longevity of vaccine-induced protective immunity and potential herd immunity. In conclusion, an integrated modeling approach can help to fully optimize a program’s impact and guide target intervention development.

### IMMUNOLOGIC BASIS FOR SCHISTOSOMIASIS VACCINES

Historically, vaccines are among the most cost-effective interventions for preventing human infectious diseases. A schistosomiasis vaccine currently does not exist, and substantial development effort would be needed. Nevertheless, strong immunologic evidence exists to support a vaccine approach for schistosomiasis control and elimination. Generally, the immune responses toward schistosome parasites have two distinct components: 1) immunopathogenesis and/or immunoregulation resulting from the release of antigens from schistosome eggs trapped in tissues, a situation that leads to granuloma formation, fibrosis, scarring, and eventually morbidity if not well controlled, or chronic inflammation and anemia; and 2) age-dependent concomitant immunity against reinfection resulting from repeated natural adult worm death over time, a process that ultimately leads to establishment of protective immunity over several years. Evidence indicates that partially protective natural immunity can develop in disease-endemic areas, and part of the protective effect of PZQ is considered attributable to the protective immunity that is generated against the adult worms killed by the PZQ. Furthermore, irradiated cercariae can confer up to 80% protection against infection in experimental animal challenge models.

Current understanding of mechanisms of protective immunity is limited. However, increased levels of IgE against adult worm antigens, eosinophilia, and IL-5 plus low levels of IgG4 antibodies to these antigens have been correlated with partial protection. CD23+ B cells have also been correlated with development of resistance to infection. In addition, *S. mansoni* studies in Brazil and Senegal demonstrated immunity to reinfection was associated with Th2 cytokine gene clusters on human chromosome 5. Resistance to reinfection was also described as associated with eosinophilia, interleukin-5 (IL-5), and IgE after PZQ treatment. Participants highlighted gaps in the current understanding of schistosome immunology and suggested that additional human immunology research is needed to better understand the two sides of the schistosome immunology coin for a better vaccine design and development. The fact that several highly efficacious recombinant veterinary vaccines against multicellular parasite infections have been demonstrated with significant efficacy in recent field trials (cysticercosis by *Taenia solium* or cystic echinococcosis by *Echinococcus granulosus*) suggested that optimism is warranted in assessing feasibility of a vaccine for schistosomiasis.

### PERSPECTIVES AND ADVANCES ON SCHISTOSOMIASIS VACCINE DEVELOPMENT

Three types of vaccines can be considered for development (in decreasing order of desirability): 1) a prophylactic vaccine to prevent or reduce infection and indirectly transmission
susceptible persons and subsequent in vivo antibody screening of immune samples from resistant and susceptible phenotypes have enabled feasible antigen screening processes to augment the global vaccine pipeline. As a result, many internal proteins, tegument surface enzymes, antigens and surface glycan antigens were presented as potential new vaccine targets. It is important, however, to point out that antigens are differentially expressed during various stages of the schistosome life cycle or disease phase, which might lead the human host to respond differently at different time points. For example, humans downregulate IgE responses to highly expressed antigens (e.g., the allergen-like protein SmTAL2), but slowly build IgE responses to others (SmTAL1, SmTAL3, and SmTAL5) during chronic infections. Responses against SmTAL1, SmTAL3, SmTAL5, and ShTAL1 have also been observed to be associated with reinfection. Therefore, antigens identified through natural immune recognition may not necessarily be the best vaccine targets. Rather, molecules that perform critical functions may be better vaccine candidates because they may represent the “Achilles heel” of the schistosome parasites. In the process of prioritizing antigens, further characterization of the biological functions and pathways in which antigens are involved should be encouraged. Modeling is also proposed as one of the approaches to examine the role of antigens in reinfection in different populations to guide early antigen selection. Understanding the complexity of antigen responses is critical, as an effective vaccine may ultimately need multiple schistosome antigens targeting several biologic pathways.

An example of a process to prioritize new antigens or vaccine candidates for preclinical development was presented: 1) post-genomically select target antigens expressed on schistosomula alone or also in adult worms using bioinformatics; 2) select promising candidates by antibody screening of cDNA libraries/protein arrays with defined serum from resistant and susceptible populations with different intensities of infection; 3) confirm candidates by using in vitro schistosomula killing assays; 4) validate antigens by differential recognition patterns by T and B cells of endemic populations classified as resistant and susceptible; 5) further characterize biological function and pathways of the antigens; and 6) conduct pre-clinical in vivo testing in animal models. Subsequently, the candidacy of a given antigen for further development as a possible vaccine would be assessed based on the above outcomes. These steps should produce a panel of highly immunogenic antigens expressed on schistosome larvae, hopefully with identified biological functions, that are ready for preclinical process development and subsequent entry into human studies.

A myriad of biological challenges still remain, e.g., the lack of appropriate animal models to evaluate vaccine efficacy early during development; the lack of a complete picture of correlates of protection in humans; the potential atopic risk of an IgE response to vaccine or parasite antigens; and numerous co-infections existing in disease-endemic areas are of potential concern. Possible antigen polymorphism issues, such as those encountered in malaria blood-stage vaccine development were also raised, although the current understanding of the Schistosoma parasite antigen diversity and polymorphism is still incomplete. Some studies suggest significant genetic diversity of the parasites and
<table>
<thead>
<tr>
<th>Schistosoma species</th>
<th>Developer</th>
<th>Vaccine</th>
<th>Target antigen proposed mechanism of action</th>
<th>Status</th>
<th>Outcomes</th>
</tr>
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<tbody>
<tr>
<td><em>S. haematobium</em></td>
<td>INSERM and Eurogentec</td>
<td>Monovalent recombinant protein with alum (Bilhvax)</td>
<td>Sh28 GST glutathione S-transferase</td>
<td>Phase I and II studies completed (phase Ia in Europe on adults, phase Ib in Senegal on children); currently in phase III trial (result due in 2013)</td>
<td>Safe and immunogenic; induced IgG1, IgG2, IgG3 isotypes, and antisera reduced GST28 enzymatic activities; induced Th2 type cytokine responses</td>
</tr>
<tr>
<td><em>S. mansoni</em></td>
<td>FIOCRUZ</td>
<td>Monovalent recombinant protein in glucopyranosyl lipid adjuvant-stable emulsion</td>
<td>Fatty acid binding protein- Sm14</td>
<td>Phase I trial completed</td>
<td>Well tolerated and safe</td>
</tr>
<tr>
<td><em>S. mansoni</em></td>
<td>Sabin Vaccine Institute</td>
<td>Monovalent Recombinant protein with adjuvant</td>
<td>Tetraspanin surface antigen; Sm-TSP-2 to affect parasite membrane biogenesis in schistosomules and adult worms</td>
<td>Preclinical process development completed, good laboratory practice toxicity study and current good manufacturing practices completed. Phase I slated for late 2013</td>
<td>Adult worm and egg burden reduction by 40–60% (mice); human IgG antibody associated with putative resistance</td>
</tr>
<tr>
<td><em>S. japonicum, S. mansoni</em></td>
<td>University of Georgia</td>
<td>DNA prime, recombinant protein boost</td>
<td>Target antigens tetraspanin (SmSj23) and glycolytic enzyme TPI (SmSjTPI); interfere with invading larva survival, leading to reduced adult worms in livestock and humans (vaccine for humans or for animals to reduce transmission to humans)</td>
<td>Field studies in water buffalo and cattle with SjTPI</td>
<td>Reduction in adult worm burden by ≤55% and egg burden by ≤57% in experimental challenge studies (with Sj23 and SjTPI); (field studies with an improved new delivery method for SjTPI ongoing in China and the Philippines)</td>
</tr>
<tr>
<td><em>S. mansoni</em></td>
<td>Texas Tech University Health Sciences Center</td>
<td>Monovalent recombinant protein with adjuvant</td>
<td>Sm-p80 calpain protein to affect parasite surface membrane renewal of tegument of lung-stage schistosomula (prophylactic) or epithelial syncytium of the adult parasite (therapeutic)</td>
<td>Animal proof-of-concept studies completed; process development ongoing</td>
<td>Worm reduction in prophylactic model: 70% (mice), 60% (baboons); egg reduction in prophylactic model: 100% (mice), 100% (baboons); showed complete elimination of egg-induced organ pathology</td>
</tr>
<tr>
<td><em>S. japonicum</em></td>
<td>Brown University</td>
<td>Monovalanet recombinant protein with adjuvant</td>
<td>Paramyosin 97-kD protein Sj97 expressed on schistosomular surface, tegument and acetabular glands, binds complement and Fc region of IgG; proposed role in host immune evasion</td>
<td>Currently early preclinical process development and proof-of-concept studies in mice and buffalo</td>
<td>Worm reduction by 52% in mice and 50% in buffalo</td>
</tr>
<tr>
<td><em>S. japonicum</em></td>
<td>Queensland Institute of Medical Research</td>
<td>Bivalent (SjIR and SjTPI) recombinant proteins with adjuvant</td>
<td>Insulin receptor SjIR targets to host insulin binding and prevent worm glucose uptake and SjTPI inhibits worm glycolysis</td>
<td>Currently testing in mice, planned in buffalo in China and the Philippines</td>
<td>Adjuvanted monovalent SjIR reduced fecal eggs in mice by 56–67%; SjTPI reduced worms by 48–52% in buffalo</td>
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polymorphism of parasite antigen proteins; others envision limited gene flow among parasites and limited diversity within the parasite genetic makeup in the field. The process development, manufacturability, and formulation of antigens were not extensively discussed during the workshop. Rather, the potential schistosomiasis vaccine manufacturing partners were explored by landscaping current vaccine manufacturers in developing countries. It is foreseeable that vaccine manufacturing partners may emerge from developing countries where schistosomiasis is prevalent and of national interest, such as Brazil. Leveraging industry partnerships and experience early in development would clearly benefit efforts to develop schistosomiasis vaccines.

There was limited discussion on the clinical development plan for a schistosome vaccine, perhaps because of lack of sufficient experience in conducting schistosome vaccine clinical trials. The series of P28GST anti-pathology vaccine trials sheds light on the potential to use egg production in animal models as a surrogate endpoint to predict clinical outcomes for either limiting pathology or blocking transmission. Early detection of active schistosomiasis, with potentially highly sensitive, advanced diagnostic tools, such as an ultrasensitive up-converting phosphor–circulating anodic antigen assay to detect even a single worm, is on the horizon. This detection will significantly help to validate vaccine efficacy accrued through reduction in worm burden or egg excretion and warrants further investigation and development. Another suggestion included the initial development of veterinary vaccines for use in reservoir hosts of S. japonicum as part of the overall product development plan for humans. The participants agreed that the immediate needs are to carefully consider a clinical development plan to ascertain the technical readiness for efficacy and safety trials of any type of schistosomiasis vaccines. Special attention should be paid to the proposed target population, efficacy endpoints and surrogate markers of protection, and applicability of laboratory-based findings or assays in the field.

Overall, the meeting participants recognized the needs to better understand immunologic mechanisms of protection, identify more target antigens (including T cell antigen candidates), and establish a unified approach to prioritize antigen candidates. Biologic characterization of parasite targets, validation of animal models for antigen discovery and vaccine evaluation, potential antigen polymorphisms that might affect vaccine efficacy differentially in the field, and the need to avoid stimulating inappropriate IgE responses to circumvent safety and regulatory issues all need to be considered early in the development process. Effort should also be made to define a clear target product profile (TPP) that includes target population and vaccine characteristics and to recognize that the TPPs for vaccines against different schistosome species will likely be distinct. The participants also noted the need to clearly articulate a better plan to move vaccine testing beyond phase I, including addressing such issues as efficacy evaluation, quantitative worm detection before morbidity is observed, approaches to detect and evaluate a partially protective vaccine (especially in-country trials around MDA program), and the downstream vaccine deployment challenge. Finally, the necessity to develop a database to share tools regarding candidate antigens, age-specific treatment outcomes, and clinical trial data was also highlighted.

CONCLUSIONS

In summary, elimination of schistosomiasis as a public health problem, a goal laid out by the WHO Roadmap, represents a challenging goal for the schistosomiasis community. To have a permanent impact, an integrated multi-functional approach involving chemotherapy, WASH, snail control, vaccines, and other innovative tools will be required. A vaccine may have synergistic benefit when combined with MDA to sustain and build upon the progress gained through broad chemotherapy campaigns, and a vaccine should be considered as the next step in pursuing disease elimination. Mathematical and computational modeling will help to guide vaccine design and elimination program strategies. Vaccine development for schistosomiasis should be pursued contemporaneously while current control efforts are scaled up. As noted during the discussions, defining a clear TPP for a desirable schistosomiasis vaccine and taking advantage of new technologies and tools available for new antigen discovery, vaccine delivery, process development, clinical research, and vaccine efficacy evaluation could all contribute to accelerated progress. A desirable vaccine should be designed to complement MDA without adding separate implementation costs. Together with all the existing tools, a newly developed schistosomiasis vaccine tailored to fit program needs would help to achieve and sustain true disease control and eventual elimination.

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