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Development of a Schistosomiasis Vaccine

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Summary

Schistosomiasis is a neglected tropical disease (NTD) of public health importance. Despite decades of implementation of mass praziquantel therapy programs and other control measures, schistosomiasis has not been contained and continues to spread to new geographic areas. A schistosomiasis vaccine could play an important role as part of a multifaceted control approach. With regards to vaccine development, many biological bottlenecks still exist: the lack of reliable surrogates of protection in humans; immune interactions in co-infections with other diseases in endemic areas; the potential risk of IgE responses to antigens in endemic populations; and paucity of appropriate vaccine efficacy studies in nonhuman primate models. Research is also needed on the role of modern adjuvants targeting specific parts of the innate immune system to tailor a potent and protective immune response for lead schistosome vaccine candidates with the long-term aim to achieve curative worm reduction. This review summarizes the current status of schistosomiasis vaccine development.

Keywords

Schistosomiasis; Vaccine; *Schistosoma mansoni*; *Schistosoma haematobium*; *Schistosoma japonicum*; Protective immunity; Neglected tropical disease (NTD)

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Introduction

Schistosomiasis continues to be a health concern since at least the ancient Egyptian Middle Kingdom period (1500 BC) [1]. Even in the 21st century, this neglected tropical disease afflicts mankind in 74 different countries and carries an estimated yearly mortality rate of 280,000 [2]. Estimates also indicate that 207 million people are currently infected and an additional 779 million people are at risk of acquiring this parasitic disease [3–5]. Based on a finding that for every egg-positive individual with schistosomes there is an egg-negative infected individual, estimates now are that between 400 million and 600 million people could be infected with schistosomes [6]. Approximately 10% of *S. mansoni* infected individuals suffer from hepatic periportal fibrosis, which can lead to portal hypertension, hepatosplenomegaly and esophageal varices; all which are hallmark clinical manifestation associated with the chronic disease [7;8]. Even mild to moderate fibrosis is correlated with poor nutritional status, anemia, fatigue, impaired cognitive ability, and increased susceptibility to infection with pathogens such as HIV-1 [9–11]. Nearly one half of the cases of schistosomiasis are caused by *Schistosoma haematobium*, the etiological agent of the urogenital form of the disease, which is endemic to Africa and the Eastern Mediterranean. The rest of the cases of schistosomiasis are mostly due to *S. mansoni* infection, the pathogen responsible for the hepatic/intestinal form of the disease, and this form is predominant in Africa, the Eastern Mediterranean, the Caribbean and South America. Additionally, a small fraction (~1%) of hepatic/intestinal schistosomiasis, known as the “Oriental” or “Asiatic” forms, is caused by a zoonotic disease from infection with the *S. japonicum* group of parasites - including *S. mekongi* in the Mekong river basin. Blood fluke, *S. japonicum* is endemic to South-East Asia and the Western Pacific region. Finally, *S. intercalatum* causes a version of intestinal schistosomiasis that has been reported in central African countries. Estimates of the total disability-adjusted life years (DALYs) attributable to schistosomiasis vary widely ranging from 3.3 million DALYs to as high as 36 million DALYs depending on the reporting sources [1, 2]. The discrepancy in DALYs may be attributed to differing and difficult assessments of various *Schistosoma*-associated disease morbidities. Despite decades of integrated control measures with improved sanitation and hygiene, this disease spectrum is still spreading into new areas of the globe and this is underscored by the recent reports of cases of schistosomiasis in Europe, in regions that were formerly schistosomiasis-free [12;13]. The current World Health Organization (WHO) treatment guidelines promoting a control strategy leading to elimination of schistosomiasis is primarily based on mass drug administration (MDA) of praziquantel (PZQ), a drug which was discovered in the 1970s. Many of the WHO Strategic Plan milestones for schistosomiasis control have been reached in targeted geographic areas such as Egypt [14] and China [15]. Despite these partial successes, clear limitations exist such as high rates of reinfection in endemic areas, the potential development of drug-resistant parasites, the effective administration of drugs requiring a large infrastructure to cover all parts of an area of endemicity, and the associated costs. These constraints reinforce the need for heightened research to develop an effective vaccination strategy to complement current treatment interventions for future control and possible elimination of this parasitic disease [16–21].

This review outlines some important aspects to consider in the context of schistosome vaccine development. The current status in the development of vaccines against the three major species of schistosomes (*S. mansoni, S. japonicum* and *S. haematobium*) that infect humans is discussed, as well as new approaches that may improve the efficacy of available vaccines.

Is the development of a schistosomiasis vaccine feasible?

Historically, vaccines are among the most cost-effective interventions for preventing human infectious diseases. A schistosomiasis vaccine currently does not exist, and extensive research effort is still needed to generate an approved vaccine for this disease. Nevertheless, strong immunologic evidence in both humans and animal models exists to support the feasibility of developing of an effective vaccine for schistosomiasis control and/or elimination [22;23]. Generally, immune responses toward schistosome parasites have two distinct components: 1) immunopathogenesis resulting from host immune responses against antigens released from schistosome eggs trapped in tissues; and 2) age-dependent, immune-resistance to reinfection which leads to protective immunity over several years. Evidence indicates that partially protective natural immunity can develop in disease-endemic areas, and that part of the protective effect of PZQ could be attributed to the protective immunity that is generated against antigens released by adult schistosomes killed by PZQ [24;25]. In addition, immunization with irradiated schistosome cercariae can confer up to 80% protection against infection in experimental animal challenge models [26;27]; as well as in non-permissive animal models like rats and rhesus macaques; worm elimination proceeds via a coordinated immune response by the host [28;29]. Furthermore, recent field trials with recombinant veterinary vaccines have shown significant efficacy against multicellular parasite infections like cysticercosis caused by *Taenia solium* [30] and cystic echinococcosis caused by *Echinococcus granulosus* [31], which suggests that we can be optimistic about the feasibility of developing an effective vaccine for schistosomiasis. However, a substantial development effort will be required if this is to become a reality sooner rather than later.

Schistosomiasis vaccine development – target profiles and advances

Despite intensive research over the last few decades to advance the development of schistosomiasis vaccine for clinical evaluation, progress in developing more promising candidates has been lackluster at best [32]. One of the reasons for this slow progress in developing an effective schistosome vaccine is due to the inherent capability of the parasites to effectively evade their host's defensive immune responses [33;34]. Nonetheless, in three separate meetings, sponsored by the National Institute of Allergy and Infectious Diseases (NIAID)[i] and the Bill & Melinda Gates Foundation[ii], the role of a schistosomiasis vaccine and other tools in context of schistosomiasis control and elimination strategies were discussed. The general consensus from the meeting was that only three types of schistosomiasis vaccines can be considered for development: 1. Most desirable: A prophylactic vaccine aimed at preventing/reducing infection rates while decreasing

[i]Neglected Tropical Diseases: Defining Opportunities to Accelerate Translational Research (March 9–11, 2011) and Schistosomiasis Vaccine Meeting (November 13, 2013), NIAID/NIH, Bethesda, MD.
[ii]Schistosomiasis Elimination Strategy and Potential Role of Vaccine in Achieving Global Health Goals Meeting, NIAID/NIH and the Bill & Melinda Gates Foundation, Seattle, WA (March 12–13, 2013).

transmission and/or leaving the host worm-free; 2. Somewhat desirable: A vaccine aimed at reducing or eliminating reinfection or transmission by interrupting female worm survival and/or egg production; or 3. Least desirable: A therapeutic vaccine to reduce disease but not affect infection or transmission [32]. It is noteworthy that an effective vaccine that targets any or more of these pathways would need to mesh with existing control strategies. Based on the discussions some of the acceptable features for a prophylactic schistosomiasis vaccine were outlined (Table 1). It was also agreed upon at the meetings that integrated modeling will help guide rational vaccine design to achieve maximum outcome in the context of existing control approaches.

immunity

Only a few vaccine candidates are under serious development with most of them still in the very early phases of preclinical feasibility evaluation. Table 2 summarizes major vaccine candidates currently in different pre-clinical and clinical stages of development. Among the candidates summarized in Table 2, a recombinant *S. haematobium* 28-kD glutathione S-transferase (r*Sh*28GST) protein produced in *Saccharomyces cerevisiae* and formulated with adjuvant [35;36], is the only vaccine in a Phase III clinical trial. Even though both Phase I and II trials have been completed for this candidate, published data for Phase I demonstrated that the vaccine is safe in healthy individuals [36]. Immunological readouts demonstrated that r*Sh*28GST is highly immunogenic and induced high titers of specific total IgG, IgG1, and IgG3 as well as inducing Th2 type cytokines such as IL-5 and IL-13. The Phase III trial evaluations of this recombinant Sh28GST are focused on combination with PZQ administration to determine if treatment can delay pathologic relapses in children infected with *S. haematobium*.

Another antigen candidate undergoing clinical evaluation is Sm14, a monovalent 14-kDa fatty acid-binding protein (FABP), designed to prevent *S. mansoni* infection [37;38]. Recombinant Sm14, produced in *Pichia pastoris*, was formulated with glucopyranosyl lipid adjuvant stable emulsion (GLA-SE) and has completed a phase I clinical trial (ClinicalTrials.gov Identifier: NCT01154049), showing that the adjuvanted Sm14 product is well tolerated, safe and highly immunogenic [39]. Vaccination stimulated anti-Sm14-IgG antibodies as well as a strong Th1 biased response as evidenced by γ-interferon production on re-stimulation of cells from individuals in vaccinated subjects [38]. Phase II trials to assess field-based immunogenicity and safety of Sm14 are planned in endemic areas of Brazil and Africa.

Schistosoma mansoni tetraspanin, a monovalent 9-kDa recombinant surface antigen (Sm-TSP-2) [40;41], is another promising candidate that is currently entering clinical Phase I (ClinicalTrials.gov Identifier: NCT02337855). Preclinical studies have shown that immunizing with Sm-TSP-2 vaccine protected mice against *S. mansoni* infection with number of adult worms recovered and egg burden reduced by 40% and 65%, respectively [40;41]. Having completed preclinical development, a GLP toxicity study and cGMP manufacturing, the Sm-TSP-2 combination on the Alhydrogel form of alum is moving into clinical testing with the added adjuvant, GLA-AF, to determine immunogenicity,

reactogenicity, and safety in healthy, non-infected adults in the United States. The study is expected to be completed by mid-2016.

Schistosoma mansoni calpain (Sm-p80) is a calcium-activated surface membrane protein [42] involved in parasite surface membrane renewal, a mechanism employed by blood-feeding helminths to evade host immunity [43]. Over the last two decades, our group has followed a systematic and methodical approach to develop Sm-p80 as a viable and effective schistosomiasis vaccine. To our knowledge, Sm-p80 is the only schistosome vaccine candidate that has been tested for its prophylactic, anti-fecundity and therapeutic efficacy in different vaccine formulations and immunization approaches (DNA vaccine alone; recombinant protein with adjuvants; and priming with DNA vaccine, followed by boosting with protein plus adjuvants) in three experimental animal models (mice, hamsters and baboons) of infection and disease [44–53]. Sm-p80 vaccine formulations in both mice and baboons induced high levels of protection and anti-fecundity effects approaching those that could only be previously achieved with the attenuated cercarial vaccine approach [44;48]. We have reported up to 70% and 60% worm reduction in mice and baboons, respectively with almost complete elimination of egg-induced organ pathology in vaccinated animals. Human correlate studies revealed Sm-p80-reactivity with IgG in human sera from individuals that are naturally resistant to schistosome infection [48]. Equally important is the absence of prevailing Sm-p80-specific IgE in a high risk/infected populations, thus minimizing the risk of hypersensitivity reaction following vaccination with Sm-p80 in humans [48;54]. It is noteworthy that the Sm-p80 vaccine has also been demonstrated to offer cross-species protection against *S. haematobium* infections in hamsters and baboons [55] as well as against *S. japonicum* infections in mice [25;56]. Pronounced reduction in *S. haematobium* adult worm burden (48%) and in tissue egg load (64%) was observed in hamsters vaccinated with recombinant Sm-p80 formulated with the adjuvant GLA-SE. Similarly, in another cross-species protection experiment, the Sm-p80 vaccine produced a 25% reduction in *S. haematobium* adult worms and an egg load reduction in the urinary bladder by 64% in vaccinated baboons [25;56]. In addition, Sm-p80 vaccine formulations were able to decrease established adult worms in a chronic infection of baboons by 10%–36%, reduce retention of eggs in tissues by 10%–57%, and decrease egg excretion in feces by 13%–33%, compared with control formulations [57]. To our knowledge, this is the first single vaccine to have demonstrated significant protection against all three major species of schistosomes that infect humans. We believe that the cross-species protective efficacy of Sm-p80 vaccine in addition to its prophylactic, therapeutic and anti-fecundity effects reinforce Sm-p80 as an excellent vaccine candidate with a potential of providing relief for both intestinal and urinary schistosomiasis. Having concluded the proof-of-concept studies in rodent and nonhuman primate animal models, the Sm-p80 based vaccine “SchistoShield®” is now being moved into cGMP compliant production in preparation for Phase I/II human clinical trials.

Another vaccine candidate currently in development is paramyosin (Sj97), a recombinant, monovalent, protein-based vaccine designed to target infection caused by *S. japonicum* in buffaloes. A transmission blocking vaccine like this could be useful in reducing infection rates in humans [58]. Immunizing mice with recombinant Sj97 induced protection against *S. japonicum* cercariae challenge and levels of protection reaching 50% have been reported in

water buffalo [58]. However, manufacturing/scalability of paramyosin has been a lingering issue which has yet to be fully resolved. A bivalent vaccine comprising SjIR (*S. japonicum* insulin receptor) and SjTPI (*S. japonicum* triosephosphate isomerase) administered with adjuvants is currently being tested in mice but the monovalent candidates have shown limited promise to date. Adjuvanted rSjIR reduced fecal eggs in mice by 56–67% [18] while immunization with a monovalent rSjTPI vaccine in buffaloes resulted in up 52% reduction in worm burden. Additionally, a cysteine peptidase-based vaccine and a cocktail of antigens have been tested in single formulations for both *S. mansoni* and *S. haematobium* and have shown very promising levels of protection (>70%) in mice [59;60]. In addition, lead candidates, Sm14 and Sm-TSP-2 have also been tested in combination with an additional antigen with the aim of enhancing protection in the murine model but this combinational antigen approach has yielded less than 50–60% reduction in worm burden [61–63]. Additionally, there are over a hundred other schistosome antigens that have exhibited some vaccine potential, almost exclusively in murine models but due to the focused scope of this review we have limited discussion to those vaccine candidates for which a broader set of efficacy data are available.

Discovery and optimization: Producing new schistosome vaccine candidates

With a lack of candidates in the clinical pipeline and the likelihood any single candidate in the current pipeline will need to be improved, other aspects of vaccine development need to be considered. These include discovery of new, promising antigens, inclusion of powerful, modern adjuvants, a focus on process development and manufacturing as tools to decrease costs, as well as having good surrogates of human efficacy that can help guide which vaccines to move further along the clinical development path.

On the antigen discovery side, efforts are being made using in-depth proteomic analysis of the surface-exposed proteins to identify additional functionally important and host accessible antigens [42;64]. Using this approach, several hundred proteins have been identified in schistosomula; interestingly, prominent proteins detected in the host-interactive apical syncytial membrane and in the sub-tegumental fractions included the previously discussed antigens Sm-p80 and Sm-TSP-2, respectively [42], reinforcing their potential as viable vaccine candidates. Proteins exposed at the surface membranes of newly transformed schistosomula are considered to be prime targets for effective vaccines for schistosomiasis [42]. This is primarily due to the observations relating to the vaccine mediated killing of schistosomula primarily in lungs [27;65]. However, recent studies have shown that in addition to elimination of juvenile worms from lungs, vaccine-mediated killing can also be achieved of established adult worms in mice [66] and in chronically schistosome-infected baboons [57].

Modern adjuvants can make the difference between success and failure of promising antigenic targets [67]. Inclusion of adjuvants in vaccine formulations can skew the immune bias of the vaccine response, enable dose and dosage sparing, can increase the quality of the immune response and overcome immune deficiencies in the young and elderly [57;68–70]. When deciding to include an adjuvant in a vaccine formulation a number of factors should be taken into account: The type of immune response desired, the regulatory pathway for the

adjuvant, antigen/adjuvant compatibility and cost of including an adjuvant. Unfortunately, in many preclinical studies Complete and Incomplete Freund's adjuvant is used as a powerful booster of responses when too little immunogenicity is seen [71]. Since this adjuvant is reactogenic it is not used in human trials so translating findings from studies using this system to future clinical candidates is not straightforward. Combining these factors leads some groups to choose TLR4 based formulations that mimic those found in late stage clinical or approved vaccines. TLR4 agonist-based formulations are the only ones in a licensed US-based vaccine, Cervarix® [72], and the recently approved malaria vaccine, MosquiRix [73]. Many of the groups in later stage development as described above are therefore using GLA, a synthetic TLR4 based agonist to skew the immune response to Th1 [74–76] in either an alum or a lipid formulation ("GLA-SE") [55;77]. While this adjuvant appears suitable in enhancing appropriate anti-schistosomal responses [55], more extensive studies of the formulations should be performed to optimize responses since the formulation can dramatically affect immunization outcomes [55;57;78], likely due to interactions of the TLR agonist, the formulated carrier, and the antigen [79].

Producing high quality, purified schistosome antigens for vaccine studies can be very challenging for a couple of reasons: Many research proteins are produced in *E. coli* which yields very low expression levels and in some cases are almost completely localized to insoluble inclusion bodies. Following purification, the protein must be refolded to an active conformation, and even then, the final protein may only have been purified to ~90% purity. Higher quality and conformationally correct preparations have been expressed in alternatives to *E. coli* expression vectors, but cost considerations and the limited capacity of contract manufacturing organizations to produce material in some of these systems is a deterrent. Efforts should aim at increasing expression levels in the current *E. coli* vector system, exploring alternative systems such as *Pichia pastoris* and *Brevibacillus*, and employing multiple polishing chromatography steps to produce at least 95% pure protein capable of eliciting the maximum protective effect. Within these limitations, our group has been able to produce and scaled up a vaccine antigen, Sm-p80, to conclude proof-of-concept studies in rodent and nonhuman primate animal models [55;57]. The Sm-p80 vaccine ("SchistoShield®") is now being moved into the next phase of GMP-compliant (cGMP) production in preparation for Phase I/II human clinical trials.

Expert Commentary

While developing the vaccine through clinical trials, markers of efficacy can be an enormous help. Vaccine development against parasitic multicellular helminth parasites in general and schistosomes in particular, has been markedly slow. This is in part because of the limited understanding of the complex interactions between the human host and these endoparasites, including the mechanisms behind protective immunity in humans [8]. Furthermore, an emerging paradigm suggests that mechanisms of protection in the permissive mouse model of schistosomiasis cannot completely be generalized to human protection [8]. Lastly, it would be sagacious before embarking onto human clinical trials to exhaustively test first tier candidates for their prophylactic and therapeutic potential in nonhuman primate models of infection and disease. There are several reasons for this cautious approach: Lebens *et al.* [80] have correctly pointed out that some of the proposed vaccination strategies based on murine

studies could have undesired effects in some individuals if taken to human clinical trials. This is partly because there is no consensus on what levels/types of immune responses are necessary to elicit a long-lasting vaccine mediated protection in humans and contradictory data have been obtained from murine and nonhuman primate models with regards to the immune correlates of protection. Therefore, when designing immunization regimens for clinical trials, data obtained through studies in the murine model should be used with caution and some thought should be given to other variables (*e.g.*, human correlates, Th1-Th2 balance etc.) to achieve optimal results in the human system.

Five Year View

Certainly, the development of a vaccine for schistosomiasis is not without challenges. However, with modern tools and a renewed interest in elimination of the disease, great progress has been made in recent years and there is increasing hope that a vaccine strategy will be successfully deployed to help eliminate the suffering and death schistosomes have brought for millennia. We anticipate that at least three schistosome vaccines (based on Sm14, Sm-TSP-2 and Sm-p80 antigens) will go through safety/efficacy human clinical trials in the next five years. Once these important milestones are reached, an effective schistosome vaccine will emerge.

Reference List

Reference annotations

* Of interest

** Of considerable interest

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Key Issues

- Vaccine development for schistosome infections is defined by a paradigm that is different from that for bacterial or viral infections. Sterilizing immunity is likely not achievable for a schistosomiasis vaccine, but immune prophylactic interventions should confer adequate levels of protection to reduce worm burdens to an intensity associated with healthy growth and development of children, the most at-risk population
- Dependence on repeated treatment with praziquantel is not adequate and despite mass treatment with praziquantel, infection rates continue to be high. This approach can have an impact on disease transmission in areas where coverage is high but will have little bearing on interrupting disease transmission. Additionally, there is always an inherent threat of development of drug resistance by the parasite
- Long-lasting reduction in the disease manifestations and transmission with current sanitation and water infrastructures in endemic areas can only be obtained through long-term protection via vaccination coupled with chemotherapy. A vaccine would contribute to the reduction of schistosomiasis morbidity through induced immune responses leading to reduced worm burdens; decreased egg production that will ultimately result in lower transmission rates
- End-point determination of efficacy/effectiveness for a schistosomiasis vaccine in humans would mainly be focused on the estimation of egg output, which would ultimately be correlated with reduction in morbidity. Increasing availability of the Circulating Anodic Antigen (CAA) assay may additionally help determine lowered worm burdens as an outcome of vaccine trials.
- Modern vaccine development considerations such as antigen discovery, adjuvant inclusions, manufacturing and scale up as well as human surrogates of efficacy should be increasing brought into this field of investigation
- An effective schistosomiasis vaccine could potentially impact up to 1 billion people

Table 1

Brief overview of Preferred Product Characteristics (PPC) developed at a colloquium of experts [NIAID/NIH, Bethesda, MD; November 13, 2013 (Mo and Colley, unpublished)] with the immediate target being reduction in morbidity, rather than sterile

Acceptable features for a prophylactic schistosomiasis vaccine	
Indication	Prevention of infection by one of the three human schistosome parasites
Target Populations	Population in endemic countries • Adults (18–59 years of age) in high-risk occupations or areas • High risk school age children (3–12 years of age)
Efficacy	Reduce at least 75% infection by one of the schistosome species (Efficacy readout: egg output and/or worm burden)
Duration of Protection	2–3 years after last dosing
Dosage	• Parenteral administration, 2 doses administration • The vaccine antigen should not react to IgE from target population
Product Criteria	Can be co-administered with local MDA/other interventions
Manufacturing	Initially suitable for Phase I study

Table 2

Schistosome vaccine candidates at different stages of preclinical and clinical development pipeline [32]

Vaccine Formulation	Target Species	Development Stage	Developer	Efficacy in animal models
Recombinant rSh28GST protein with adjuvant (Bilharvax)	*S. haematobium*	Phase III	Inserm & Eurogentec	50% reduction in tissues / 60% to 77% reduction in excreted eggs from monkeys when adjuvanted with BCG or Complete Freund's [36;81–83]
Recombinant Sm14 protein in GLA-SE	*S. mansoni*	Phase I trial completed	Fiocruz	50% reduction of worms in mice when given with RIBI adjuvant [37;38;84]
Recombinant Sm-TSP- 2/ Alhydrogel® with GLA-AF	*S. mansoni*	Phase I trial underway	Sabin Vaccine Institute	Reductions of 57% and 64% for mean adult worm and liver egg burdens in mice, with fecal egg counts reduced by 65–69% when adjuvanted with Freund's [40;41]
Sm-p80 recombinant protein in GLA-SE (SchistoShield®)	*S. mansoni* *S. haematobium* *S. japonicum*	Proof-of-concept in rodents and nonhuman primate; GMP production/IND- filing	Texas Tech University Health Sciences Center	70% and 60% protection in mice and baboons respectively. Elimination of tissue egg pathology in baboons, vaccine-mediated killing of adult worms and potent cross-species protection [44;48;55–57;85]
DNA prime, recombinant protein boost (Sj23 and SjTPI)	*S. japonicum,* *S. mansoni* *S. haematobium*	Field studies in water buffalo and cattle	Jiangsu Institute of Parasitic Diseases/ University of Georgia	Worm burdens reduced by 21% - 32 %; liver egg burden reductions of 48% to 52% in goats when protein adjuvanted with complete Freund's [86–89]
Recombinant protein paramyosin (Sj97) with adjuvant ISA206	*S. japonicum*	Proof-of-concept in water buffalo	Brown University	Worm burden reduction in buffalo 50% [58]