

# Schistosome Infections: An Indian Perspective

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## ABSTRACT

Schistosomiasis is an endemic helminthic disease of human. Schistosomes display considerable biodiversity in habitat, host range, and epidemiology globally. In spite of the noticeable presence of sero-positivity for schistosomal antibody and passage of schistosome eggs in human faeces, Indian subcontinent has always been considered as a low risk region for human schistosomiasis. Several species has been described in India which may have association with human infection and cercarial rash. Although sporadic cases are not uncommon, the status of human schistosomiasis in India is not well investigated. In this review different aspect of schistosomal infection in human in India has been described briefly.

**Keywords:** Bilharziasis, Cercarial dermatitis, Schistosomiasis

## INTRODUCTION

Schistosomiasis is one of the oldest known parasitic infestations described in historical records. It affects about 200 million people worldwide. On an average 85% of these cases are indigenous to African continent [1]. However, it had not caught attention of the scientific community until German scientist Theodor Bilharz first described the presence of adult schistosomes in portal vein of a man at autopsy [1,2]. Schistosomes are unique member of Class Trematoda. In contrast to other trematodes, these adult worms are dioecious, parasitize venous systems and produce non-operculated eggs [1]. The fork tail cercaria of schistosomes develops in snail and infect human by skin penetration.

While *Schistosoma haematobium*, *S. mansoni*, *S. guineensis* and *S. intercalatum* are the anthropophilic species widespread in Africa, these are not common in Asia. Instead, *S. japonicum*, *S. mekongi*, and *S. malayensis* are prevalent in Asian countries [1]. Classically schistosomiasis had been a disease of the poor and rural population in tropical countries. However, significant change in its geographical distribution has been observed in recent years [3]. Advancement in health and hygiene as well as snail control measures and chemotherapy has eliminated the threat from several endemic countries. On the contrary, population movement from endemic zones and expansion of natural habitat of snail associated with unplanned establishment of dam and irrigation projects has resulted in emergence of newer endemic foci [4]. The status of human schistosomiasis in India is not well established. India has always been considered as a non-endemic country for human schistosomiasis. The non-existence of intermediate host of anthropophilic schistosomes in India is believed to be the principal reason which precludes the natural lifecycle of these schistosomes in Indian subcontinent [2]. However, at least three endemic foci of human schistosomiasis had been described in India previously and sporadic autochthonous cases and cercarial dermatitis are also not uncommon [5-8]. Moreover, several unique schistosome species of animals are prevalent in India [3]. The co-existence of several different species of schistosomes may result in newer hybrid strains pathogenic to man and the risk associated with these species as a potential source of human infection needs further research [3, 9].

## Schistosome Taxonomy and Human Schistosomes

Members of genus *Schistosoma* belong to superfamily Schistosomatoidea of the suborder Strigeata and are commonly termed as

blood-fluke because of their habitat in blood vessels in vertebrate hosts [1]. The conventional method of classifying these flukes was epidemiological and morphological characteristics like the geographical distribution, morphology of eggs and specificity and range of hosts [10]. Based on it, four groups, i.e. *S. japonicum* group, *S. indicum* group, *S. mansoni* group and *S. haematobium* group were described. In recent years, the extensive use of internal transcribed spacer region of rRNA and mitochondrial gene has categorized schistosomes in six clades, i.e. *S. japonicum* clade, *S. hippopotami* clade, proto-*S. mansoni* clade, *S. mansoni* clade, *S. haematobium* clade and *S. indicum* clade [10]. It is evident from the cladogram that the theory of origin of schistosomes in Africa and subsequent spread to Asia has weak phylogenetic basis. Considering the basal niche of *S. japonicum* clade in phylogenetic tree, authors have suggested alternate hypotheses of the evolution of schistosomes. According to it, the ancestral schistosome which was closely related to *S. japonicum*, originated in Asia and spread to Africa giving rise to African schistosome species [10].

Among 23 known species of schistosome, only seven are capable of infecting human. African anthropophilic schistosomes are *S. haematobium*, *S. mansoni*, *S. guineensis* and *S. intercalatum*. While *S. guineensis* and *S. intercalatum* are mainly confined to Africa, the former two species have wider distribution. *S. haematobium* is prevalent in Africa and the Middle East [1]. In addition to this, *S. mansoni* is also widespread in the Caribbean islands and South America. *Bulinus spp.* of snail act as intermediate host for *S. haematobium*, *S. guineensis* and *S. intercalatum* and *Biomphalaria spp.* for *S. mansoni*. On the other hand, the three anthropophilic species of *S. japonicum* clade has different snail hosts (*Oncomelania spp.*, *Robertsia spp.* and *Neotricula aperta* serve as intermediate host for *S. japonicum*, *S. malayensis* and *S. mekongi* respectively) and cause intestinal schistosomiasis in South East Asian countries. *S. malayensis* primarily affect rat (*Rattus muelleri*) and is considered as a zoonotic disease [1, 11, 12]. Human infection infrequently occurs in Malaysian aborigine foci of sylvatic transmission.

## Pathogenesis of Schistosomiasis

The pathogenic changes in schistosomiasis depend on interplay between host and parasite factors. Schistosomes display a variety of virulence factors i.e. tegument proteins schistosomal complement inhibiting protein (SCIP-1), phosphatidylcholine immunosuppressive neuropeptides and soluble egg antigen (SEA) [4]. Three types of

complex immune interaction occurs between host and parasite, i.e. immune evasion (allowing development of schistosome to adult worm in host vasculature), immune response to eggs (facilitating excretion of eggs) and partial resistance to new infection by schistosome larvae [1]. Tegument proteins incorporate host antigens, such as HLA, blood group antigens, serpins & immunoglobulins and evade host immune response by masking with host antigens. Moreover, the worm actively shed tegument. Consequently, activation of immune response to shed tegument, helps the worm to escape from immune response and also gives partial acquired resistance to new infection [4]. Tegument binds with Fc region of antibodies and SCIP-1 with serum complement proteins, rendering them ineffective. Phosphatidylcholine and neuropeptides impair the activity of macrophages and T cells respectively and thus protect the adult worm from cell mediated immunity [13]. Recently, a tegumental phosphodiesterase has been reported to be an essential factor for establishing infection [14].

*S. haematobium* reside in the vesicle venous plexus and primarily associated with bladder, ureter, renal and rectal pathology. Owing to its habitat in mesenteric veins *S. mansoni* and *S. japonicum* cause hepatosplenic and intestinal lesions. While cercarial dermatitis represents the initial phase of infection caused by migrating cercaria, the pathognomonic lesion caused by adult worms is egg granuloma. A zone of granulomatous inflammation develops surrounding the schistosome eggs trapped in host tissue as a consequence of delayed hypersensitivity response to SEA secreted profusely from the eggs [1,13]. In acute stage, the granuloma is exuberant, cellular (monocyte, macrophage, neutrophils, lymphocytes, plasma cells, epithelioid cells, giant cells and fibroblasts) with perivascular eosinophilia deposits and focal necrosis. Egg granuloma helps in excretion of eggs and also limits the damage to adjacent tissue from secreted egg products. While absence of this granulomatous response results in rapid tissue damage from secreted antigens of trapped eggs, an exaggerated response is associated with excessive extracellular matrix deposition, fibrotic changes and vascular obstruction [4]. TH1 and TH2 both responses have implications in egg granuloma formation. Lack of TH2 response in IL-4 & IL-10 knocked out mice was found to produce smaller granuloma, but also had early organ damage and mortality [4]. During chronic infection, host immune system achieves a balance between TH1 and TH2 response which is known as immunomodulation. It results in decrease in the size of granuloma without compromising its function to reduce tissue injury and efficient egg destruction.

Periportal and peribulbar fibrosis (known as Symmer's clay pipe stem fibrosis), portal hypertension, hepatosplenomegaly and esophageal variceal hemorrhage are typically found in hepatic involvement [4]. Urinary schistosomiasis includes mucosal or submucosal ulceration, patches, granuloma, polyps and immune complex mediated glomerulosclerosis. Stasis from urinary obstruction often leads to urinary tract infection and calculi [13]. While bowel wall thickening, ulceration, inflammatory pseudopolyps, abscess, fibrosis, stricture and fistula are common in schistosomiasis involving small and large intestine, patients with pulmonary schistosomiasis suffers from fibrosis, pulmonary arterial hypertension, corpulmonale and right heart failure [4]. Lung involvement is secondary to hepatosplenic schistosomiasis, where opening of collateral shunts allow the eggs to embolise in lung bypassing liver. Involvement of cerebral and vertebral veins is manifested as seizure, transient increase in intracranial pressure and hemiplegia.

### Risks of Human Schistosomiasis in India

The lifecycle of schistosome are essentially dependent on its intermediate host. Schistosomes are digenean flukes. A single miracidium larva can generate numerous infective cercariae through sporocyst in snail [9]. Hence, in absence of snails it cannot develop further. The abundance of aquatic bodies like rivers, ponds, dams

and irrigated fields in India provides ideal environment for freshwater snails. Furthermore, contamination of water bodies with human and animal faeces and urine, unhygienic practice of using river or pond water directly for drinking and domestic purposes along with poor sanitation, lack of vector control measures adds greater risk of spreading schistosomiasis in India [3]. There are several factors that may help this infection to persist unnoticed. Owing to its uncommonness, diagnosis of human schistosomiasis in India is challenging and requires a high index of suspicion while clinically evaluating patients. Schistosomiasis is a disease of the poor and underprivileged people who lack social awareness and medical facilities. As a consequence of chronicity and vague symptoms associated with intestinal or urinary schistosomiasis, it is likely that the patients in rural India hardly seek medical attention. Accordingly, actual incidence is expected to be under reported. Last but not least, population migration from endemic areas associated with the hazard of introduction of human schistosomes continues to be a significant threat in India [2].

Indian subcontinent harbors seven novel species of schistosomes infecting animals. Among them, *S. indicum*, *S. spindalis* and *S. bomfordi* was first described by Montgomery in 1906, followed by discovery of *S. incognitum* by Chandler, *S. nasale* by Rao, *S. nairi* by Mudaliar et al., and *Orientobilharziadattai* by Dutt et al., [3,15]. In addition, *O. turkestanicum* and *O. harinasutai* had also been described in buffaloes in India [3]. Dutt and Srivastava contributed to existing knowledge of schistosomiasis in India by identifying *O. turkestanicum* from an endemic village in Srinagar, describing its lifecycle and the snail host *Lymnaea auricularia* [16]. While *S. indicum*, *S. spindalis* and *S. nasale* are members of *S. indicum* clade, *S. incognitum* and *O. turkestanicum* belong to Proto - *S. mansoni* clade [10].

Although currently the common species of schistosomes pathogenic to human has not been identified to persist in India as endemic foci, there are evidence that an active focus of *S. haematobium* persisted in past in Gimvi village of Ratnagiri district of Maharashtra [6,17]. However, controversies exist regarding the species identification of schistosome of Gimvi. The intermediate hosts of Indian schistosome species are listed in [Table/Fig-1].

Schistosome species	Intermediate host
<i>S. indicum</i> ,	<i>Indoplanorbis exustus</i>
<i>S. spindalis</i>	<i>Indoplanorbis exustus</i>
<i>S. bomfordi</i>	Unknown
<i>S. incognitum</i>	<i>Indoplanorbis exustus</i> <i>Lymnaea luteola</i>
<i>S. nasale</i>	<i>Indoplanorbis exustus</i> <i>Lymnaea luteola</i>
<i>S. nairi</i>	Unknown
<i>O. dattai</i>	<i>Indoplanorbis exustus</i> <i>Lymnaea luteola</i>
<i>O. turkestanicum</i>	<i>Lymnaea auricularia</i>
Schistosome of Gimvi village	<i>Ferrissia tenuis</i>

[Table/Fig-1]: Genera of snails acting as intermediate hosts for schistosomes in India

The freshwater snails are believed to be a critical biological factor in schistosomal infection in India. The absence of *Bulinus sp.* is assumed to be the main reason that urinary schistosomiasis due to *S. haematobium* could not set foot in India even after repeated exposure of this agent in the form of infection imported from endemic countries by soldiers during first and second World War [2]. Several species of snails have been tested and found to show exceptional resistance to miracidium of *S. haematobium*. An account of these infection experiments are summarized in [Table/Fig-2] [8,18-22].

Reports of infection experiments	Findings	Reference
Soparkar	While studying the cercarial fauna of the snails in and around Bombay, 17 species of animal schistosome cercariae (no human schistosome cercaria) was found in common snails. Miracidia of <i>S. haematobium</i> failed to establish infection in these snails.	[18]
Annandale et al.,	Tested 1532 common snails of 11 species which were found negative for human schistosome cercariae and were also resistant to miracidia of <i>S. haematobium</i> .	[19]
Khaw	While studying the cercarial fauna of common snails, two animal schistosome cercariae were found in snails i.e. <i>S. indicum</i> infesting <i>I. erustus</i> and <i>S. incognitum</i> infesting <i>L. luteola</i>	[20]
Gadgil et al.,	Identified <i>F. tenuis</i> as the intermediate host of <i>S. haematobium</i> in the endemic focus in Gimvi village	[21]
Gadgil	Succeeded in establishing infection in laboratory-bred <i>F. tenuis</i> snails with miracidia of human schistosome of Gimvi village and raising the adult worms in both mice & hamster from the cercariae emerged from infected snails.	[22]
Srivastava et al.,	In the endemic foci of Lahager village, Madhya Pradesh, <i>L. luteola</i> snails were found to be parasitized by furcocercous cercaria (likely to be <i>S. haematobium</i> )	[8]

**[Table/Fig-2:]** Infection experiments with snails to determine intermediate hosts for schistosomes in India

### Evidence of Human Infection

Hatch reported a case of urinary schistosomiasis in an Englishman who was admitted in European General Hospital, Bombay in 1878 [23]. However, this first known case of human schistosomiasis in India was not an indigenous case. The patient had been in Arab and Egypt and likely to have acquired the infection from these endemic countries. In subsequent years, Hatch published a record of about 12 cases of human urinary schistosomiasis and its diagnostic features based on his observation in Jamsetjee Jejeebhoy hospital, Bombay [24]. However, the first autochthonous case in an Indian aborigine was reported in 1903 [25]. Several sporadic cases have been reported thereafter from different parts of the country and also three endemic foci have been identified [Table/Fig-3] [6, 8, 17, 23-38].

Maharashtra state holds an important place in history of schistosomiasis in India. In middle of twentieth century, the discovery of endemic focus of human schistosomiasis was a breakthrough in schistosomiasis research in India. The pioneer work of Gadgil and Shah established the epidemiology and lifecycle of *Schistosoma spp* of Gimvi. Based on the infection experiments with common snail species existing in the area, they reported *F. tenuis* as the natural intermediate host of schistosome [6,21]. Although controversies exist on the taxonomy of this species of schistosome, Gadgil and Shah reported it as *S. haematobium* [21]. A resurvey in 1958 showed decrease in overall incidence of infection in Gimvi. In addition to this, two endemic foci of human schistosomiasis were discovered from Madras (Tirupparankundaram village, Madurai district) [7] and Madhya Pradesh (Lahager village, Raipur district) [8]. However, with the elimination of foci of schistosomal infection, the number of human infection reduced significantly.

### Cercarial Dermatitis in India

Another facet of human health hazard by schistosome species is cercarial dermatitis or swimmer's itch. Although it is an emerging water-borne non-communicable disease prevalent among rural and tribal population of India, it is often neglected, unrecognized and under-reported owing to lack of access to adequate diagnostic & health care facilities [5]. Usually non-human schistosomes (birds

Reports of human schistosomiasis	Findings	Reference
Hatch	First case of human schistosomiasis in India	[23]
Hatch	Findings in 12 patients of urinary schistosomiasis	[24]
Powell	First indigenous case of human schistosomiasis in India	[25]
Sewell	Schistosomiasis in a British soldier	[26]
Christophers et al.,	Polymorphism of eggs: both <i>S. haematobium</i> as well as <i>S. spindle</i> type eggs were present in urine of a native Indian patient from Madras.	[27]
Wardrop	Reported 5 cases of which 2 were indigenous	[28]
Hooton	One indigenous case from Rajkot, Gujarat	[29]
Harkness	Urinary schistosomiasis in an Englishman, infection probably acquired in India	[30]
Milton	Urinary schistosomiasis in a British soldier in Secunderabad, infection probably acquired in India	[31]
De Mello	Urinary schistosomiasis in a Indian boy from Goa	[32]
Andreasen et al.,	Urinary schistosomiasis in a Indian soldier who was posted in Pune, Maharashtra	[33]
De Sa et al.,	First case of urinary schistosomiasis in an Indian girl from Gimvi village of Ratnagiri District, Maharashtra. This was the index which led to the discovery of this endemic focus.	[17]
Gadgil et al.,	Findings of survey in Gimvi village- 46% villagers had urinary schistosomiasis with hematuria as the most prominent finding.	[6]
Gadgil et al.,	An indigenous case <i>S. haematobium</i> infection from Nasik district	[6]
Dhanda	In a routine stool examination in Delhi, 4 out of 500 stool samples showed schistosome eggs	[34]
Santhanakrishnan et al.,	Identified Tirupparankundaram village, Madras as endemic focus	[35]
Srivastava et al.,	Identified Lahager village, Madhya Pradesh as endemic focus. 53 out of 263 urine samples showed haematuria, and one had eggs suggestive of <i>S. haematobium</i> .	[8]
Amonkar et al.,	Reported a case of squamous carcinoma of the bladder induced by urinary schistosomiasis	[36]
Savardekar et al.,	Reported a case of squamous intraepithelial neoplasia after <i>S. haematobium</i> infection	[37]
Sahu et al.,	Reported a case of tubal schistosomiasis associated with ruptured ectopic pregnancy	[38]

**[Table/Fig- 3:]** Human schistosomiasis cases reported in India

and animal schistosome) are mainly attributed to this intense inflammatory pruritic skin condition. When cercaria of these parasites emerge from their snail hosts and penetrate skin of patients, they induce inflammatory response to eliminate parasites trapped in the skin [12]. In a recent study, the prevalence of it varied from 2.1% and 12.5% during the year with highest infection rate during winter and the rainy season [5]. Agarwal et al., have reported incidence of cercarial rash in Jabalpur, Madhya Pradesh which was unrecognized and misinterpreted by health practitioners and local people [39]. In another study, water bodies of five selected locations of Ratnagiri district of Maharashtra were screened to investigate the occurrence of snails and cercaria [40]. Among nine species of snails *I. exustus* was most common. Although previously Gadgilet al. had reported *F. tenuis* to be the intermediate host for human schistosome species of Gimvi village, only *I. exustus* and *L. luteola* snails were found to have schistosome infection in that region [40].

## CONCLUSION

The status of human schistosomiasis has been an issue of great controversy. Most countries situated within the same parallel belt of longitude as India has human schistosomiasis in endemic form. The absence of snails of *Bulinussp* and resistance of common snails to miracidia of human schistosomes are implicated as the main reason of relative absence of human schistosomiasis in India. However, the discovery of endemic foci and sporadic cases of human infection indicate toward the possibility that indigenous snails may serve as an alternate intermediate host of human schistosome. Poorly developed healthcare system and lack of awareness in rural and tribal areas are important factors which precludes the assessment of status of schistosomiasis in human as well as in animals.

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