Review Article

Cryptosporidium species in HIV-infected individuals in India: An overview

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ABSTRACT

Cryptosporidium spp. are a major cause of diarrhoea in developing countries mainly affecting children and HIV-infected individuals with low CD4 counts. The infection is self-limiting in immunocompetent hosts, but can be severe and persistent in the immunocompromised and malnourished. Treatment is less than optimal and no vaccine is currently available. In the West, the ability of this protozoan parasite to survive in the environment for a long duration and cause explosive outbreaks in susceptible populations has led to its inclusion as a category B pathogen for biodefence. Reports on the prevalence of cryptosporidial diarrhoea in HIV-infected adults from different parts of India from the mid-1990s have ranged from 0.7% to 83% in symptomatic and from 1.4% to 57% in asymptomatic individuals, with very high rates in both groups in the northeastern states. Several studies in India have also documented a correlation between CD4 count < 200 cells/cmm and symptomatic cryptosporidiosis. Among children with diarrhoea, the prevalence of cryptosporidiosis has ranged from 1.1% to 18.9%. Other susceptible populations studied include patients with malignancies and transplant recipients. Molecular tools have permitted speciation and genotyping, leading to more detailed epidemiological studies than were possible with microscopy alone. Using these methods, the common cryptosporidial species reported to affect both HIV-infected adults and children in India are *C. hominis* and *C. parvum*. With easier access to antiretroviral therapy for Indian patients with HIV, the effect on the prevalence of cryptosporidiosis and aetiology of HIV-related diarrhoea remains to be seen. Therefore, data from different parts of India form a necessary baseline against which the effect of antiretroviral therapy can be evaluated.

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INTRODUCTION

Cryptosporidium spp. are apicomplexan parasites that cause protracted and life-threatening diarrhoea in HIV-infected individuals.[1] This protozoan pathogen is also an important cause of diarrhoea in children all over the world with a high associated morbidity and mortality.[2] Cryptosporidiosis in humans is mainly attributable to 2 of the 14 identified species: *Cryptosporidium hominis* (previously known as the *C. parvum* human genotype) and *Cryptosporidium parvum* (or bovine genotype). *C. hominis* is found almost exclusively in humans, whereas *C. parvum* is found in domestic livestock, wild animals as well as humans. Transmission occurs by direct person-to-person spread, ingestion of contaminated food or water, or contact with infected animals.

The life-cycle of *Cryptosporidium* spp. is completed within the small intestine and colon of the host, with the developing stages associated with the luminal surface of the intestinal epithelial cells, where it remains intracellular but extracytoplasmic.[3] Infection in a new host occurs following the ingestion of as few as 10 oocysts (ID_{50} 132 oocysts), as evidenced in studies on healthy adult volunteers.[4] This is followed by the release of motile sporozoites in the intestine which invade the epithelial cells. The invasive process involves Gal/GalNAc epitopes of sporozoite surface glycoproteins[5] and recruitment of the host actin cytoskeleton to form a parasitophorous vacuole.[3] A feeder organelle at the site of attachment is believed to function as a portal to allow nutrients from the host cell to the parasite. Parasite surface glycoproteins documented to be involved in the invasion and attachment process include gp900, gp40/15 and circumsporozoite surface ligand (CSL).[6,7] Asexual (merogony) and sexual reproduction of the parasite occurs within the extracytoplasmic vacuole, resulting in merozoites that infect adjacent epithelial cells and the production of sporulated thin-walled and thick-walled oocysts. Thin-walled oocysts can excyst endogenously, resulting in autoinfection, which, along with repeated first-generation merogony, helps to explain the mechanism of persistent infections in patients with AIDS. The spherical, thick-walled, environmentally hardy oocysts (3–6 μm in diameter), shed in the faecal material of the infected host are immediately infectious, unlike other coccidian parasites, and hence can be transmitted from person to person. The alterations in the intestinal structure and physiology that lead to the pathogenesis of cryptosporidiosis include rapid loss of the microvillus border, shortening and fusion of the villi and lengthening of the crypts resulting in malabsorption due to loss of membrane-bound digestive enzymes, decreased absorption, reduced glucose–NaCl absorption and increased chloride anion secretion. Proinflammatory cytokines specifically IFN-γ and TNF-α also contribute to the pathogenesis of cryptosporidiosis by increasing the production of prostaglandins, neural peptides and reactive nitrogen intermediates, disruption of

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the epithelial barrier leading to a leaky and dysfunctional epithelium and alteration of solute transport leading to osmotic diarrhoea.[7]

Immune responses involved in mediating resistance to infection with this parasite are not well understood, but evidence obtained from immunodeficient animal models have shown that a Th_1 response involving primarily TCR αβ+ CD4+ lymphocytes, IFN-γ and interleukin (IL)-12 play a major role in the control of *C. parvum* infection.[8] The susceptibility of patients with HIV/AIDS to this pathogen and resolution of cryptosporidiosis following immune restitution underscores the importance of CD4+ T cells. Humoral immune response to oocyst lysates, as well as to specific glycoprotein antigens, have been characterized in volunteer and seroepidemiological studies.[6] Serological response to cryptosporidial antigens coincident with resolution of symptoms has been associated with some protection, and pre-existing antibodies associated with decreased severity and duration of infection, but these antibody responses may only be markers of other cell-mediated protective responses. Increasing evidence for the protective effect of an initial innate response has also been documented. These include studies on mannose-binding lectin in Haitian children with cryptosporidiosis,[9] toll-like receptors mediating response to infection via IL-8 and NF-κB in epithelial cell lines,[10] IL-15 mediated elimination of parasites by NK cells[11] and IL-18 potentially mediating secretion of antimicrobial peptides.[12]

Owing to its sequestered location within the host cell, ability to set up an auto-infective cycle in the host, innate antimicrobial resistance and ability to affect several host species, this parasite has a large survival advantage over other enteric pathogens.[13] The potential to cause explosive and massive water-borne outbreaks involving entire townships, due to the ability of oocysts to survive for months in the environment, has also been well documented in developed countries. The largest outbreak was in Milwaukee, USA and affected an estimated 403 000 persons in 1993.[14] As there is a distinct potential for intentional contamination of water supplies, the Centers for Disease Control and Prevention (CDC) has included this parasite as a category B pathogen for biodefence. Although nitazoxanide has been recently licensed for the treatment of cryptosporidiosis in children[15] and immuno-competent individuals in most countries including India, there is still no effective treatment for cryptosporidiosis in patients with AIDS, unlike other coccidian causes of diarrhoea such as *Isospora* spp. and *Cyclospora* spp., which can be treated with trimethoprim–sulphamethoxazole. No vaccine is available to prevent *Cryptosporidium* infection in susceptible populations. The urgent need for development of tools for early detection, treatment and prevention of cryptosporidiosis, especially in developing countries, is highlighted by its inclusion in the 'Neglected Diseases Initiative'[16] in September 2004. Documentation of the epidemiological profile of cryptosporidiosis in HIV-infected individuals and the burden of disease in India will aid in planning and instituting appropriate control measures and plan future studies on the transmission dynamics of this pathogen.

PROTOZOAN DIARRHOEA IN HIV

Diarrhoea is the most common gastrointestinal symptom reported in HIV-infected individuals, with the incidence increasing when CD4 counts drop below 200 cells/cmm.[17] In India, recent sentinel surveillance estimated that there were around 2.47 million people living with HIV/AIDS (PLHA) and the 4 states of Andhra Pradesh, Maharashtra, Tamil Nadu and Karnataka contributed 63% of all reported cases.[18] HIV-infected individuals are subject to a cumulative lifetime incidence of diarrhoea estimated at up to 100% in developing countries and 30%–70% in developed countries[19] with chronic diarrhoea affecting up to 76% of patients with AIDS.[20] The common enteric opportunistic pathogens described are cytomegalovirus, *Cryptosporidium* spp., *Isospora belli*, Microsporidia, *Mycobacterium avium intracellulare* and, more recently, *Clostridium difficile*. Many diarrhoeal episodes remain undiagnosed and this could be attributed to unidentified agents or primary HIV enteropathy. In India, *Entamoeba histolytica* and *Giardia lamblia*, along with *Cryptosporidium* spp. and *I. belli* have been reported as the most common causes of diarrhoea. However, most studies have focused only on protozoan aetiology.[21,22] The other pathogens that have been reported in Indian patients with HIV-related diarrhoea include *Cyclospora*, *Strongyloides stercoralis*, *Blastocystis hominis*, *Dientamoeba fragilis*, Microsporidia, *Campylobacter jejuni*, *Salmonella*, *Shigella* and diarrhoeagenic *E. coli*.[22–28] The risk factors associated with diarrhoeal disease due to parasites in Indian patients include CD4 counts <200 cells/cmm, previous history of diarrhoea, use of public toilets, lower education and socioeconomic status, residence in slums and exposure to animals.[29–32] In children with HIV in India, chronic diarrhoea has been reported in 6.8%–42% of cases but very few studies examined the specific aetiology of diarrhoea.[33] Pathogens reported to cause diarrhoea in HIV-infected children include rotavirus, *Shigella*, *Campylobacter*, *E. coli*, cryptosporidiosis, isosporiasis, cytomegalovirus and atypical mycobacteria.[33,34]

CRYPTOSPORIDIOSIS IN HIV

Cryptosporidiosis is a substantial threat to HIV-infected individuals and in developed countries such patients have an estimated risk of infection of around 10%.[35] Patients can have chronic watery diarrhoea that can last for >2 months and shed oocysts in the stool during the entire period, resulting in severe dehydration, weight loss and malnutrition, extended hospitalizations and mortality.[1,36] Other symptoms include abdominal cramps, anorexia, nausea, vomiting, fatigue and low-grade fever. Cryptosporidiosis remains a major risk to the immunocompromised because of the lack of effective, specific therapy. Therapeutic approaches for cryptosporidiosis in the past have included macrolide antibiotics, paramomycin, rifaximin, octreotide and immunotherapy, among others. Although nitazoxanide is licensed for use in immuno-competent patients, a recent meta-analysis found it to be ineffective in patients with HIV.[36] AIDS patients with crypto-sporidiosis also have a significantly shorter duration of survival from the time of diagnosis.[35] In the immunocompromised host, *Cryptosporidium* spp. is the most commonly isolated pathogen in the biliary tract in patients with AIDS cholangiopathy.[37] A few studies have reported other sites of infection including the pancreas and lungs.[38]

In India, there have been reports from the mid-1990s on the prevalence of symptomatic cryptosporidiosis in HIV-infected adults from different parts of the country, ranging from as low as 0.7% to as high as 81% (Table I). A high prevalence of ~80% was reported from a study in Imphal[44] and another in Maharashtra[41] but both had very small sample sizes. Most of these studies were done on HIV-infected adult patients and used modified acid-fast staining of concentrated stool samples. However, the data on prevalence are highly varied and could reflect geographical differences, as well as differences in the populations being studied especially with respect to socioeconomic status and access to potable water. A few recent studies that also did enzyme-linked immunosorbent assay (ELISA) and polymerase chain reaction (PCR) for

TABLE I. Prevalence of cryptosporidiosis in HIV-infected individuals in India (1995–2008)

Author	Place	Year	Cases	*n*	% symptomatic	% asymptomatic
Kumarasamy *et al*.[25]	Chennai	1995	Adults	100	16	–
Giri *et al*.[39]	Northern India	1995	Adults and children	134	4	–
Anand *et al*.[40]	Manipur	1996	Adults (i.v. drug users)	150	46.6	–
Ghorpade *et al*.[41]	Karad, South Maharashtra	1996	–	305	83.3 †	–
Lanjewar *et al*.[26]	Mumbai	1996	Adults	77	31	–
Anand *et al*.[42]	Manipur	1997	Adults (asymptomatic i.v. drug users)	–	–	57.8
Ananthasubramaniam *et al*.[43]	Chennai	1997	–	108	6.5	0
Agarwal *et al*.[44]	Imphal	1998	Adults		81.8*	–
Mukhopadhya *et al*.[23]	Vellore	1999	Adults	111	9.8	6
Prasad *et al*. [24]	Lucknow	2000	Adults, chronic diarrhoea	59	11.5	–
Mohandas *et al*. [27]	Chandigarh	2002	Mostly adults	120	22.6	1.49
Joshi *et al*.[45]	Mumbai	2002	–		8.5	–
Kumar *et al*.[28]	Chennai	2002	Adults	152	13.7	8
Vajpayee *et al*.[46]	New Delhi	2003	Adults	421	18.6	–
Shenoy *et al*.[47]	Mangalore	2003	–	120	17.5	–
Singh *et al*.[48]	Manipal	2003	Adults	–	–	43
Sharma *et al*.[49]	New Delhi	2004	Adults	135	9.3	–
Banerjee *et al*.[22]	Vellore	2005	–	258	15.5	–
Mamatha *et al*.[50]	Manipal	2005	–	140	18.57	–
Sadraei *et al*.[30]	New Delhi	2005	Adults	200	42.1	38.1
Adhikari *et al*.[51]	Nepal	2006	Adults	196	–	5.2
Muthusamy *et al*.[29]	Vellore	2006	Adults	534	25.2	4.7
Attili *et al*.[21]	Varanasi	2006	–	–	5.71	–
Becker *et al*.[32]	Bangalore	2007	Adults	298	0.7	2
Dwivedi *et al*.[31]	New Delhi	2007	Adults	75	66.6	8
Ramakrishnan *et al*.[52]	Madurai	2007	Adults	80	28.7	–
Vignesh *et al*.[53]	Chennai	2007	Adults	245	2.9	–
Jayalakshmi *et al*.[54]†	Coimbatore	2008	–	89	12.4	–
Gupta *et al*.[55]	New Delhi	2008	Adults	113	20.6	2.5
Kaushik *et al*.[56]†	Chandigarh	2008	Adults	206	25.2	14.9

*Very small sample sizes † Multiple detection methods used (microscopy/antigen detection/polymerase chain reaction)

detection[54,56] found a higher sensitivity for PCR and lower for antigen detection ELISA compared with microscopy, which also contributed to variability in prevalence rates. Several studies in India have documented mean CD4 counts in these patients with most studies showing that symptomatic cases had CD4 counts <200 cells/cmm and asymptomatic cases had CD4 counts >300 cells/cmm, thus reinforcing the importance of CD4 T cells in mediating resistance to this pathogen.[21,29,31,39] A study from Delhi that stratified patients based on their CD4 counts showed that *Cryptosporidium* was the commonest parasite seen in 46% of patients with counts <200 cells/cmm. The prevalence of cryptosporidial diarrhoea (56%) was also significantly higher when CD4 counts were <200 cells/cmm compared with patients with higher CD4 counts (40%).[30]

Antiretroviral therapy (ART) greatly influences the outcome of cryptosporidiosis both indirectly by immune restitution and increase in CD4 counts[57] and by the direct effect of protease inhibitors on oocyst shedding,[58] resulting in a sustained therapeutic effect after follow up. However, despite the use of highly active antiretroviral therapy (HAART), HIV-infected patients can still present with coccidian diarrhoea, possibly due to non-compliance with medications, viral resistance to drugs or decreased bioavailability of drugs.[59] Relapses after discontinuation of HAART have also been documented.[60] In India, recently HAART has become available at an affordable cost through the government's ART roll out programme started in 2004. This programme now covers around 56 000 people and a recent study from Chennai on the current non-nucleoside reverse transcriptase inhibitors (NNRTI)-based therapy initiated when CD4 counts were <250 cells/cmm showed a substantial increase in life expectancy rate and that it was cost-effective.[61] Another study examining the effect of HAART on the incidence of opportunistic infections in India has found a decrease in both opportunistic infections and tuberculosis in patients on therapy. Hence, increased access to HAART has impacted the natural history of HIV infection.[62] Although western data indicate a shift in the aetiology of diarrhoea in HIV-infected patients[19] and there seems to be a decrease in opportunistic infections in a single study, the effect of HAART on the occurrence of cryptosporidiosis and aetiology of diarrhoeal disease in Indian patients remains to be examined. Antiretroviral drug-induced side-effects resulting in diarrhoea in Indian patients will have to be taken into account.

MOLECULAR TYPING OF CRYPTOSPORIDIAL SPECIES

The differentiation of species is done based on polymorphisms at several loci including β-tubulin, TRAP-C1, TRAP-C2, ITS1, polythreonine repeat (Poly-T), dihydrofolate reductase (DHFR) and heat shock proteins (Hsp).[63] However, currently most workers do a nested PCR and restriction fragment length polymorphism (RFLP) at the small subunit 18S RNA gene (SSU rRNA) as it provides consistent and reproducible results.[63] Extensive polymorphisms among *C. hominis* isolates at the *Cpgp40/15* locus have been used as an epidemiological tool for subgenotyping in several studies.[64] The importance of differentiating between species using molecular tools is highlighted by several recent findings. These include a report of longer periods of oocyst shedding in *C. hominis* compared with *C. parvum*-infected patients in Peru,[65] significantly higher oocyst shedding and greater growth shortfalls

at 6 months post-infection in children with *C. hominis* in Brazil[66] and longer duration of symptoms, higher rate of asymptomatic infection and lower CD4+ cell count in HIV-infected patients with *C. hominis* infection compared with *C. parvum* infection in Tanzania.[67] Another recent study showed that infection with *C. hominis*, but not *C. parvum*, was associated with an increased risk of non-intestinal sequelae in immunocompetent adults and in children.[68] Studies in human volunteers have shown that *C. hominis* is highly infectious in immunocompetent adults with an infectious dose as low as 10 oocysts and an attack rate of 62%.[4] Studies in Vellore on cryptosporidial diarrhoea in children showed that *C. hominis* infections were associated with more severe diarrhoea.[69] Therefore, identifying the species and subgenotypes to differentiate between anthroponotic and zoonotic strains and documenting the molecular epidemiology of crypto-sporidiosis will help plan interventional measures to prevent and treat cryptosporidial infections. In the West, these molecular tools have been used to characterize water-borne epidemics.[13]

Although cryptosporidiosis is endemic in tropical countries, only a limited number of isolates have been typed from developing countries, especially from HIV-infected people. Data on genotypes and species in HIV-infected individuals in India are limited to a single study from Vellore which showed a cryptosporidiosis prevalence of 25% among HIV-seropositive individuals with diarrhoea and 4% in those without diarrhoea. Although *C. hominis* was the most common species identified accounting for 64% of positive cases, a strikingly high prevalence of potentially zoonotic species was seen including *C. parvum, C. meleagridis, C. felis* and *C. muris* in symptomatic as well as asymptomatic HIV-infected adult patients, but no significant animal contact was found in the cases with potentially zoonotic infections. The subgenotypes identified in these cases were *Cpgp40/15* subtypes II, Ia, Ib, Ic, Id and If. Previous studies have also indicated that immunocompromised individuals are susceptible to a wider range of zoonotic species and genotypes and that host factors must play a role in controlling susceptibility to these divergent parasites. Other *Cryptosporidium* spp. reported to infect humans, mainly immunocompromised hosts, include *C. meleagridis, C. felis, C. canis* and *C. muris*.[70] In developed countries, zoonotic infections are usually due to contact with domestic pets but studies from endemic countries such as Thailand and India have shown a high prevalence of zoonotic species of up to 50% with no significant contact with pets in these cases.[29,71] A recent study from Delhi has documented a history of contact with animals in 87% of patients with diarrhoea and in 32% with cryptosporidiosis. However, genotyping to identify zoonotic cryptosporidial species was not carried out.[31] Studies on bovine cryptosporidiosis in Kolkata and Punjab have found prevalence rates ranging from 26% to 50% in calves with diarrhoea and 8.5% to 25.7% in those without diarrhoea, the predominant species being *C. parvum*[72,73] with a high mortality rate of 35%.[74] These studies indicate that, in addition to causing disease and death in livestock and other animals, the high prevalence of and asymptomatic cryptosporidial infections for these animals could serve as a reservoir of infection for susceptible human hosts in India.

Among the other coccidian parasites, *Isospora belli* has also been reported frequently with prevalence rates ranging from 2.5% to 60% in patients with diarrhoea. More recent studies in India show lower prevalence rates than *Cryptosporidium* (probably due to prophylactic treatment with trimethoprim–sulphamethoxazole)[21,29,31,52,56] but a few have recorded higher prevalence rates.[53,55] *Cyclospora*, on the other hand, has been isolated very infrequently from HIV-infected individuals in India with low prevalence rates ranging from 0.98% to 6.5% in symptomatic individuals.[23,27,29,49]

OTHER SUSCEPTIBLE POPULATIONS

In developing countries, cryptosporidiosis is more common in malnourished than well-nourished children and the consequences are more severe in the former than in the latter, possibly because of impaired T cell responses. Studies from South America suggest that both symptomatic and asymptomatic cryptosporidiosis in children are associated with growth faltering with slower recovery in symptomatic infection[75] and even a single episode predicts a subsequent increased risk of diarrhoeal disease.[76] Watery diarrhoea, vomiting, anorexia and weight loss are the commonest symptoms. In India, a number of studies have reported *Cryptosporidium* spp. in diarrhoeal stool samples of children with positivity rates ranging from 1.1% to 18.9%. Asymptomatic cryptosporidiosis rates were between 0% and 9.8% (Table II) and in a study on children with malabsorption, the parasite was seen in 14%.[100] Only 3 studies till date have used PCR for identification indicating that actual infection rates may be significantly higher. In a community-based study from Vellore, the 2 most common species identified in children with diarrhoea were *C. hominis* (81%) and *C. parvum* (12%). Five subgenotypes were identified at the *Cpgp40/15* locus and subgenotype Ia predominated among *C. hominis* isolates.[69] In a hospital-based study from Kolkata, of 40 samples identified as positive with microscopy over 5 years, 35 were *C. hominis*, 4 were *C. parvum* and 1 was *C. felis* indicating a similar species distribution.[98] A recent hospital-based study from Secunderabad on adults and children also found that *C. hominis* (69%) was the most common genotype.[99]

A study on patients undergoing allogeneic bone marrow transplantation (BMT) in Vellore identified *Cryptosporidium* spp. in 7 of 65 cases and found a higher mortality in patients with enteric pathogens[101] but in more recent studies from the same centre, *Cryptosporidium* was identified in 2.9% of adult and 1.7% of paediatric allogeneic BMT recipients.[102,103] The rates of infection were similar to those in the West, possibly attributable to good infection control strategies. A study on renal transplant recipients in northern India identified cryptosporidial diarrhoea in 16.6% of patients.[104] Only one study from Varanasi, evaluating risk factors for cryptosporidiosis in the geriatric age group, has been done in which 18.3% of patients had cryptosporidiosis among which 66% had a history of close contact with animals.[105]

CONCLUSIONS

The current literature regarding cryptosporidiosis and HIV in India is limited to a few epidemiological studies and several hospital-based surveys with limited information on infecting species, host risk factors and transmission dynamics of this disease. More information on the impact of *Cryptosporidium* on human health and a better understanding of its epidemiology will help in realizing the importance of this parasite, which could lead to increased research on and prevention and control of this parasite. In the HIV-infected population in India, the determinants of disease are multifactorial and documenting the interplay of epidemiological, clinical, immunological and molecular parameters will play a key role in understanding the natural history of infection and the impact of ART.

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TABLE II. Prevalence of cryptosporidiosis among children in India (1985–2007)

Author	Place	Year	Age (years)	*n*	% symptomatic	*n*	% asymptomatic
Mathan *et al.*[77]	Vellore	1985	<3	682	13.1	418	9.8
Malla *et al.*[78]	Chandigarh	1987	<12	375	1.3	–	–
Das *et al.*[79]	Calcutta (Kolkata)	1987	<12	402	5.9	–	–
Sengupta *et al.*[80]	Calcutta (Kolkata)	1988	<5	244	6.1	274	1
Singh *et al.*[81]	Varanasi	1988	0.5–3	180	3	100	0
Pherwani *et al.*[82]	Mumbai	1989	<5	77	4.4	165	0
Subramanyam *et al.*[83]	Bhubaneswar	1989	<8	566	13	167	0
Pal *et al.*[84]	Calcutta (Kolkata)	1989	<5	266	5.6	294	1.2
Reinthaler *et al.*[85]	Idukki	1989	<10	100	6	50	3
Kaur and Diwan[86]	Delhi	1991	<2	100	5	50	0
Uppal and Natarajan[87]	New Delhi	1991	<10	201	4.9	–	–
Das *et al.*[88]	Calcutta (Kolkata)	1993	<12	289	5.5	274	1.1
Nath *et al.*[89]	Varanasi	1993	<5	607	3.8	529	1.8
Jindal *et al.*[90]	Amritsar	1995	<3	–	1.3	–	–
Shetty *et al.*[91]	Manipal	1995	<5	106	1.8	–	–
Sethi *et al.*[92]	Chandigarh	1999	<12	355	1.4	–	–
Nagamani *et al.*[93]	Secunderabad	2001	< 3	–	6	–	–
Kamalaratnam *et al.*[94]	Vellore	2001	<3	–	–	249	7.2
Ballal and Shivananda[95]	Manipal	2002	<5	77	15.6	100	3
Kaur *et al.*[96]	Delhi	2002	<5	127	18.9	–	–
Palit *et al.*[97]	Kolkata	2005	<12	–	–	14	2.3
Das *et al.*[98]	Kolkata	2006	<5	–	4.6	–	1.2
Nagamani *et al.*[99]	Secunderabad	2007	<12	681	7.6	–	–

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ANNOUNCEMENT

Sri Aurobindo Ashram, Delhi Branch will organize the 2nd Study Camp on **'Mind–Body Medicine and Beyond'** for doctors, medical students and other health professionals at its **Nainital Centre (Madhuban)** from 8 to 15 June 2009. The camp consisting of lectures, practice, and participatory and experiential sessions, will help the participants get better, feel better and bring elements of mind–body medicine into their practice. The camp will be conducted by Professor Ramesh Bijlani, MD, former Professor, All India Institute of Medical Sciences, founder of a mind–body medicine clinic at All India Institute of Medical Sciences, and the author of *Back to Health through Yoga.* The camp contribution of Rs 3000 per head includes food and stay on a twin-sharing basis. For more details, contact the ashram reception in Delhi (011-2656-7863) or e-mail Dr Bijlani (rambij@gmail.com).