CHAPTER 1

Coinfection of *Schistosoma* (Trematoda) with Bacteria, Protozoa and Helminths

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Contents

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Abstract

This review examines coinfection of selected species of *Schistosoma* with bacteria, protozoa and helminths and focuses on the effects of the coinfection on the hosts. The review is based mainly on tables that contain the salient information on the coinfecting organisms in vertebrate hosts. Further explanation and clarification of the tables are given in the text. A table is also provided that gives synoptic information on the 37 species in the 19 genera considered in this review. Coinfection studies with *Schistosoma* species and the other organisms were considered in six tables plus the accompanying text. Considerations of the *Schistosoma* interactions with another species of organism include studies on coinfection with *Plasmodium*, with protozoa other than *Plasmodium*; with *Salmonella*, with bacteria other than *Salmonella*; and with *Fasciola*, with helminths other than *Fasciola*.

Numerous factors were found to influence the effects of coinfection on the vertebrate host, including organisms and hosts used in the studies, order and time interval between the first and the second infection, studies on natural versus experimental hosts, dosage of the infectious agents, strains and pedigrees of the parasites, age of hosts at time of exposure to the infectious agents and age of hosts at the time of necropsy. Overall, a prior infection with *Schistosoma*, particularly a patent infection, often has an effect on the subsequent infection by a protozoan, bacterium or other helminth. In relatively few cases, a prior infection with *Schistosoma* decreased the severity of the subsequent infection as with *Helicobacter pylori*, *Fasciola hepatica*, *Echinostoma* or *Plasmodium*, the latter only exhibiting this behaviour when coinfected with *Schistosoma haematobium*. More often, however, a prior infection with *Schistosoma* increased the severity of the second infection as with *Leishmania*, *Toxoplasma gondii*, *Entamoeba histolytica*, *Staphylococcus aureus* or *Salmonella*. In some of these coinfection studies, the increased severity of the subsequent infection was associated with a specific, prolonged form of the disease in humans, which has implications for patient treatment and recovery. Additional research is needed, particularly on *Schistosoma* coinfections which currently have a small body of research and are current

problems in human populations. Examples of such *Schistosoma* interactions include the genera of *Mycobacteria*, *Leishmania*, *Staphylococcus*, *Necator* and *Strongyloides*. Hopefully, future studies will elucidate valuable new information on the interesting subject of coinfection of *Schistosoma* with other organisms.

1.1. INTRODUCTION

This review examines coinfection of selected species of *Schistosoma* with various other organisms, that is, helminths, protozoa and bacteria. We originally intended to examine coinfection interactions of schistosomes with viruses, but because of the voluminous literature on that topic, we have excluded such information from this review. The schistosomes are water-borne digeneans of global concern. Species in the genus *Schistosoma* have been well studied in terms of single infections in their vertebrate hosts, but less information on schistosomes coinfected with other organisms is available. In this review, we examine the salient studies that link species of schistosomes with protozoa, bacteria and other helminths.

Areas of concern in our review include infections in the wild and also experimental infections in the laboratory. Important aspects of our review include the interactions of the schistosome of concern with the coinfecting organism in terms of physiological, immunological, ecological and epidemiological consequences. Important to these studies are factors such as the order of infection, that is, was the host first infected by the schistosome or the other organism. The time sequence when known between the first and the second infection is given. Results of coinfection within the host are considered to determine the effects of such infection on the pathogenicity of the host. We also address the issue of whether the coinfection increased, decreased or had no effect on the severity of the infection in the host. The implications of the above concerns are important in both human and veterinary medicine.

Our review has numerous tables as in Fried and Abruzzi (2010), and tabular information is followed by text to clarify and extend the information in the tables. We emphasize coinfection events between the schistosome of interest and a single other organism, that is, another helminth, protozoan or bacterium. Numerous studies exist on polyparasitism (multiparasitism) in which naturally infected hosts are infected with three or more parasites. Such studies are not included in this review unless they relate directly or tangentially to an examination of the relationship of two coinfecting organisms in a host. Case reports, when relevant, are also referred to in the text. The effects of larval parasite dosage on coinfection are not included in this review. In experimental studies, the larval dosage cannot always be correlated with the number of

parasites recovered in the host; also, many authors have failed to provide such information in their original papers. The effect of parasite dosage is usually unknown in natural coinfection studies.

The literature in our tables ranges from January 1, 1972 to March 1, 2011. Helminthological Abstracts (1972–to date) and ISI Web of Science (1975–to date) were searched in multiple ways: firstly, broadly using the general terms with the truncation symbol ''*'' to pick up variant endings: (*interact** or *coinfect** or *co-infect** or *concomitant** or *concurrent** or ''*mixed infect**'' or ''*double infect**'') and *schistosom**. Additional studies were identified by searching for pairs, such as ''*schistosom** and *fasciol**''. Studies identified this way were checked for references to other publications within our time period. All English language papers were examined in full. Some earlier reviews on coinfections helped us decide what should be covered in our review; the most important earlier reviews were those of Graham (2002), Cox (2001), Chieffi (1992) and Christensen et al. (1987). Additional reviews were noted as relevant to the section under review. All specific entries in each table except Table 1.1 are in reverse chronological order and are numbered accordingly beginning with number 1. The text of our chapter refers to the entry numbers and summarizes major trends in the coinfection interactions between the organisms of interest. We concentrated on the major effect of each pairing on the vertebrate host in comparison to the relevant control group. Coinfection studies that were mainly serologic, chemotherapeutic or used for vaccine development were not included in our review; we have not included studies that examined the effects of worm self- versus cross-fertilization in coinfected hosts.

Most readers will be familiar with the organisms discussed in this review. However, Table 1.1 provides a brief synopsis of the highlights of organisms covered in Tables 1.2–1.7. Further information on these organisms can be obtained from introductory texts on parasitology and microbiology or by using pertinent web sites.

1.2. COINFECTION OF SPECIES OF *SCHISTOSOMA* AND *PLASMODIUM*

This section is concerned with coinfection studies on species of *Schistosoma* and *Plasmodium*. A total of 32 papers were selected for inclusion in Table 1.2. Of these, 13 were experimental studies using mice as hosts (entry numbers 1, 5, 8, 11, 18, 24–26, 28–32) and the remaining 19 papers described naturally occurring coinfections in human populations (entry numbers 2–4, 6, 7, 9, 10, 12–17, 19–23, 27). The organisms studied in these papers were two species of *Schistosoma* and five species of *Plasmodium*. Both *Schistosoma* species, *S. mansoni* and *S. haematobium*, and three of the

TABLE 1.1 A guide to species considered in Tables 1.2–1.7

Genus	Species included in tables	Remarks (based on single infections)	Table(s)
Schistosoma	*S. bovis*, *S. douthitti*, *S. haematobium*, *S. intercalatum*, *S. japonicum*, *S. mansoni*	Mainly three species concerned with human infection, that is, *S. mansoni*, *S. japonicum*, and *S. haematobium*; dioecious adults live in blood vessels with hepatic portal and intestinal vessels as the main sites for *S. mansoni* and *S. japonicum* and venous blood vessels of the urogenital system for *S. haematobium*; also listed in this column are the animal forms *S. bovis*, *S. douthitti*, and *S. intercalatum*	1.2–1.7
Protozoa			
Entamoeba	*E. histolytica*	*E. histolytica* is a causative agent of amoebic dysentery and intestinal and extraintestinal amoebiasis; the organism spreads by oral-faecal contamination	1.3
Leishmania	*L. donovani*, *L. donovani infantum*, *L. major*, *L. mexicana mexicana*	Infective stages are transmitted to humans by the bite of sandflies in the genus *Phlebotomus*, and invade and develop in selected macrophages of vertebrate hosts	1.3
Plasmodium	*P. falciparum*, *P. malariae*, *P. berghei*, *P. chabaudi*, *P. yoelii*	These vector-borne sporozoans are transmitted to humans and animals by the bite of anopheline mosquito; the last three species listed in column 2 are mainly murine forms	1.2
Toxoplasma	*T. gondii*	This apicomplexan (sporozoan) species is transmitted to humans mainly by animal and faecal contact; it invades many cell types including macrophages and myocytes	1.3

(*continued*)

TABLE 1.1 (*continued*)

Genus	Species included in tables	Remarks (based on single infections)	Table(s)
Trypanosoma	*T. brucei*, *T. cruzi*	These are blood and tissue flagellates; *T. brucei* is transmitted by the bite of the tsetse fly (*Glossina* sp.) and *T. cruzi*, the intracellular myocardial form, is transmitted by the bite of triatomid bugs	1.3
Bacteria			
Helicobacteria	*H. pylori*	*H. pylori* is a gram-negative, microaerophilic bacterium. It inhabits various regions of the stomach and is linked to duodenal and gastric ulcers; in some cases, it induces stomach cancer	1.5
Mycobacteria	*M. avium*, *M. bovis*, *M. paratuberculosis*, *M. ulcerans*	Several of these species are in the *M. tuberculosis* complex including *M. paratuberculosis*, *M. bovis*, and *M. bovis*-BCG; Buruli ulcer is associated with *M. ulcerans*; organisms in this complex are aerobic, non-motile, acid-fast, and gram-positive	1.5
Salmonella	*S. enterica* (numerous serotypes as discussed in Table 1.4)	These are gram-negative facultative rod-shaped bacteria usually referred to as enteric bacteria, with many strains, subspecies and variants. Major diseases associated with these bacteria are salmonellosis and typhoid fever	1.4
Staphylococcus	*S. aureus*	This species has many variants that are gram-positive and form grape-like clusters; toxins associated with some *S. aureus* strains cause food poisoning	1.5

Trematodes other than schistosomes			
Echinostoma	*E. caproni*, *E. paraensei*	Echinostomes infect the intestinal tract of humans and cause intestinal distress; seriousness of the infection often relates to worm burdens. This is mainly a food-borne infection for humans, although some infections occur following ingestion of water-borne cercariae	1.7
Fasciola	*F. hepatica*, *F. gigantica*	*F. hepatica* is a liver fluke of humans and animals and is transmitted to hosts that eat contaminated (mainly raw) vegetation, for example, watercress. Adults develop in the liver and bile duct of the host and can induce severe pathology	1.6
Nematodes			
Ancylostoma	Unidentified species	A genus of hookworm with species that infect human and non-human hosts via the skin; larvae wander through many organs prior to final entry in the intestines where they develop to adult worms. Infection is associated with anaemia in the host	1.7
Ascaris	*A. lumbricoides*, *A. suum*	These species infect hosts (human or pig, respectively) when they swallow eggs in contaminated soil; larvae migrate through the body and eventually develop as adults in the intestine where they may cause intestinal blockage and other types of pathology	1.7
Brugia	*B. pahangi*	A type of filarid introduced into humans via the bite of mosquitoes. Adult filarids live in lymph nodes; larvae in the blood and lymphatics	1.7

(*continued*)

TABLE 1.1 (*continued*)

Genus	Species included in tables	Remarks (based on single infections)	Table(s)
Heligomosomoides	*H. polygyrus*	A common rodent trichostrongyloid with a direct life cycle; it is often referred to as *Nematospiroides dubius*; it is used as a model nematode in laboratory mice, often for immunological studies	1.7
Necator	*N. americanus*	The best known human species is *N. americanus*. This is the predominant hookworm in the tropics and is also a cosmopolitan species. Larvae enter by penetrating the skin of the host and take a circuitous route through the body before colonizing in the small intestines; adult worms can cause anaemia and other severe pathologies in hosts	1.7
Strongyloides	*S. venezuelensis*	A rodent form of strongyloid often used as a model to study human strongyloidiasis. An important model for studies on the human pathogen *S. steralis*	1.7
Trichuris	*T. muris*, *T. trichuris*	The main species of concern is *T. trichuris* or human whipworm, which is usually a mild pathogen causing lower intestinal damage depending on the number of worms in the host. *T. muris* is a mouse strain often used in experimental studies	1.7

TABLE 1.2 Coinfection studies on species of *Schistosoma* and *Plasmodium*

Entry number	Reference	Species of trematode	Species of coinfecting organism	Experimental (E) or natural (N) infections in vertebrate hosts	Time between coinfections	Comments
1	Bucher et al. (2011)	*Schistosoma mansoni*	*Plasmodium berghei*	(E) C57BL/6 mice	Sm followed by Pb 8–9 wk later	Coinfected (Co) mice had decreased malarial brain pathology compared to mice with single Pb infection; pre-existing infection by Sm did not prevent severe malaria or death but influenced the course of malarial pathology; outcomes were unrelated to cerebral malaria (CM)
2	Courtin et al. (2011)	*S. haematobium*	*P. falciparum*	(N) 7- to 19-year-old human	Unknown	Coinfection had an additive effect on cytokine levels; Co hosts had higher IL-10 levels than individuals with single infections and may increase risk of Pf disease or death
3	Midzi et al. (2010)	*S. mansoni* or *S. haematobium*	*P. falciparum*	(N) 5- to 15-year-old humans	Unknown	Co children had lower haemoglobin levels and a higher prevalence of anaemia than single or non-infected children; Co aggravates anaemia

(*continued*)

TABLE 1.2 (*continued*)

Entry number	Reference	Species of trematode	Species of coinfecting organism	Experimental (E) or natural (N) infections in vertebrate hosts	Time between coinfections	Comments
4	Sangweme et al. (2010)	*S. mansoni* or *S. haematobium*	*P. falciparum*	(N) 6- to 17-year-old humans	Unknown	Co hosts had higher overall prevalence of malaria parasites with greater incidence and densities of gametocytes than children with single Pf infections; Co may have implications for malaria disease severity and transmission dynamics
5	Waknine-Grinberg et al. (2010)	*S. mansoni*	*P. berghei*	(E) ICR mice	Sm followed by Pb 4 or 7 wk later	Infection with Sm followed by Pb 7 wk later led to reduction in CM and was correlated with a Th2 response; no malarial reduction after 4 wk of coinfection; protection from CM appeared to be a function of Sm parasite load and timing
6	Mouk et al. (2009)	*S. mansoni*	*P. falciparum*	(N) 8- to 10-year-old humans	Unknown	Co children had a lower mean % of HLA-DR(+) Tact and a lower mean level of memory Treg cells than children with single Sm infections; imbalances in T lymphocyte subsets may be related to differential morbidity or course of infection in Co hosts

7	Nmorsi et al. (2009)	*S. haematobium*	*P. falciparum*	(N) 1- to 15-year-old humans	Unknown	Co children had lower parasitaemia and higher haemoglobin levels than children with single Pf infection; concentrations of IL-4, IL-5, IL-8, and IFN-y were elevated in Co children compared with the Pf group; Co altered Th1/Th2 profile, which may have protected against severe malarial attacks or death
8	Sangweme et al. (2009)	*S. mansoni*	*P. yoelii*	(E) BALB/c mice	Sm followed by Py 14 days later	Hosts with patent Sm infection had a delayed response to Py infection with increased Py peak parasitaemia and mortality in typically self-resolving Py infections; hepatosplenomegaly was more marked in Co than single infected mice; timing of Py infection after Sm infection may be critical to disease outcome and pathology

(*continued*)

TABLE 1.2 (*continued*)

Entry number	Reference	Species of trematode	Species of coinfecting organism	Experimental (E) or natural (N) infections in vertebrate hosts	Time between coinfections	Comments
9	Wilson et al. (2009)	*S. mansoni*	*P. falciparum*	(N) 4- to 17-year-old humans	Unknown	Co children had higher plasma levels of sTNF-RII and IL-5 than non- or single Pf infected children; IL-10 levels were higher in Co than non-infected children; elevated levels of IL-12p70, IL-10, IL-13 and sTNF-RII were associated with hepatosplenomegaly and malaria infection; levels may be due to augmentation of the inflammatory response in liver and spleen
10	Faye et al. (2008)	*S. mansoni*	*P. falciparum*	(N) 1- to 15-year-old and some older humans	Unknown	In children aged 1–14 years, Co hosts had higher Pf densities than children with single Pf infection; highest malarial densities occurred in Co children less than 5 years old; in children aged 15 years and older, Co had lower Pf densities than children with single Pf infection

11	Laranjeiras et al. (2008)	*S. mansoni*	*P. berghei*	(E) BALB/c mice	Sm followed by Pb infection 24 wk later	Co mice had increased malarial parasitaemia and decreased survival compared to single Pb infected mice. Skewed immune profile induced by chronic Sm infection might affect the course of the Pb infection and the acquisition of malarial immunity
12	Okafor and Elenwo (2007)	*Schistosoma* sp.	*Plasmodium* sp.	(N) Newborn–14-year-old humans	Unknown	Co children had lower concentrations of haemoglobin than single infected or non-infected children; concentrations were lowest among children aged 10–14 years than other age groups
13	Lyke et al. (2006)	*S. haematobium*	*P. falciparum*	(N) 4- to 14-year-old humans	Sh followed by acute Pf infection	Co children, 4–8 years old, had lower IL-6 and IL-10 levels compared to children with single Pf infection; IL 4 levels were inversely correlated with time to malaria infection in all 4- to 8-year-old children; children with underlying Sh infection had polarized Th2 response which may have modulated the incidence and severity of subsequent infection with Pf

(*continued*)

TABLE 1.2 (*continued*)

Entry number	Reference	Species of trematode	Species of coinfecting organism	Experimental (E) or natural (N) infections in vertebrate hosts	Time between coinfections	Comments
14	Arinola (2005)	*S. haematobium*	*P. malariae* or *P. falciparum*	(N) 6- to 14-year-old humans	Unknown	Co children had lower malaria parasite density and severity, and higher levels of leukocyte migration inhibitory factor and reactive oxygen species than single Pm or Pf infected children
15	Briand et al. (2005)	*S. haematobium*	*P. falciparum*	(N) 3- to 15-year-old humans	Unknown	Children with light Sh infection had lower Pf densities than children with single Pf infection; parasite density decreased with age and was lower in girls than boys; immune responses varied according to the stage and intensity of infection
16	Lyke et al. (2005)	*S. haematobium*	*P. falciparum*	(N) 4- to 14-year-old humans	Sh followed by Pf infection	Children aged 4–8 years with asymptomatic Sh infection showed delayed time to clinical malaria infection with fewer number of malarial episodes and lower mean parasite densities than comparably aged children with single Pf infection; no

						protective association seen in 9- to 14-year-old children; underlying Sh infection was associated with protection against clinical malaria for younger children only
17	Diallo et al. (2004)	*S. haematobium*	*P. falciparum*	(N) 7–15 years-old and 30 years and older humans	Unknown	Co children had higher levels of IFN-gamma and TNF-RII than children with single Pf infection; Co adults showed an increase in IL-10, IFN-gamma, TGF-beta and sTNF receptors; coinfection appeared to unbalance the regulation of inflammatory factors that played a key role during malaria infection in an age-dependent manner
18	Legesse et al. (2004)	*S. mansoni*	*P. berghei*	(E) Swiss albino mice	Sm followed by Pb 7 wk later	Mice with Sm had increased parasitaemia and mortality from Pb compared to mice with single Pb infection; delayed reduction and or clearance in parasitaemia was also noted in Co hosts; mortality from Pb in Co mice was 67% compared to 20% in single Pb mice

(*continued*)

TABLE 1.2 (*continued*)

Entry number	Reference	Species of trematode	Species of coinfecting organism	Experimental (E) or natural (N) infections in vertebrate hosts	Time between coinfections	Comments
19	Sokhna et al. (2004)	*S. mansoni*	*P. falciparum*	(N) 6- to 15-year-old humans	Unknown	Children with the highest Sm egg loads (>1000 epg) had a greater incidence of malarial attacks than children without or with lower Sm infections; malaria attacks were higher in children with the lowest egg load than in children with medium Sm egg burden; parasite load of Sm may affect Pf infection, but this may not be a simple linear relationship
20	Mwatha et al. (2003)	*S. mansoni*	*P. falciparum*	(N) 8- to 16-year-old humans	Unknown	Sm-infected children with hepatosplenomegaly had higher levels of antimalarial antibodies than Sm-infected children without hepatosplenomegaly; in particular, antimalarial IgG1 and IgG3 levels were higher in Sm positive hepatosplenic children; antimalarial antibodies appeared to be associated with the development of hepatosplenomegaly in Sm-infected children

21	Egwunyenga et al. (2001)	*S. mansoni*	*Plasmodium* sp.	(N) near-term pregnant human females	Unknown	In two of three study areas, Co pregnant females were more likely to have severe splenomegaly than those with single malaria infection
22	Friis et al. (2000)	*S. haematobium*	*Plasmodium* sp.	(N) 7- to 11-year-old humans	Unknown	Co children were less likely to have splenomegaly than those infected with single malaria infection; malaria-induced splenomegaly may have impaired the establishment of Sh infection or Sh infection may have modified the affect of malaria infection on the development of splenomegaly
23	Mutapi et al. (2000)	*S. haematobium*	*P. falciparum*	(N) 5- to 17-year-old humans	Unknown	Co children produced more anti-schistosome IgE and IgG3 antibodies than single infected Sm children; malaria infection influenced cytokine environment and the production of both isotypes
24	Yoshida et al. (2000)	*S. mansoni*	*P. chabaudi*	(E) C57/BL6 and A/J mice	Sm followed by Pc 8 wk later	C57/BL6 mice with coinfection showed greater susceptibility, parasitaemia and mortality than mice with single Pc infection;

(*continued*)

TABLE 1.2 (*continued*)

Entry number	Reference	Species of trematode	Species of coinfecting organism	Experimental (E) or natural (N) infections in vertebrate hosts	Time between coinfections	Comments
						A/J mice with coinfection had a higher parasitaemia than Pc-infected C57/BL6 mice, but Sm infection protected A/J mice from mortality through induction of increased IFN-gamma production
25	Helmby et al. (1998)	*S. mansoni*	*P. chabaudi*	(E) C57BC/6 mice	Sm followed by Pc 8 wk later	Co mice developed greater Pc parasitaemia, showed lower RBC counts and lower TNF-a production than mice with single Pc infection; Co mice had 8–13% mortality compared with no mortality among single Pc-infected mice; coinfection altered the immune responses to existing and new infections
26	Rahman (1990)	*S. mansoni*	*P. chabaudi*	(E) male CBA mice	Sm followed by Pc 4 or 7 wk later	Co mice had lower blood parasitaemia than single Pc-infected mice; Co mice had greater parasitaemia when coinfected at 4 wk compared to 7 wk; antibody response to Pc was delayed in mice coinfected at 4 wk while mice coinfected at 7 wk

						had consistently higher response; timing of coinfection affected the malaria response
27	Kassim and Ejezie (1982)	*S. haematobium*	*P. falciparum*	(N) 7- to 14-year-old humans	Unknown	Co children showed no association with frequency of blood group types compared to children infected with single Sh or Pf infection
28	Lwin et al. (1982)	*S. mansoni*	*P. chabaudi* or *P. yoelii* or *P. berghei*	(E) CBA/Ca mice	Sm followed by Pc, Py, or Pb 4–12 wk later	Co mice with patent (8 wk) Sm infection had lower Pc parasitaemia than mice with single Pc infection; Co mice with patent (8 wk) Sm infection had higher Py parasitaemia than mice with single Py infection; Co mice with 8 wk Sm infection had Pb parasitaemia comparable to mice with single Pb infection; pre-patent 4-wk Sm infection had no effect on Pc, Py, or Pb parasitaemia
29	Long et al. (1981)	*S. mansoni*	*P. chabaudi*	(E) CBA/Lac mice	Sm followed by Pc 49 days later; Pc followed by Sm 5 days later	When Sm was followed by Pc, Co mice had lower maximum malaria parasitaemia than mice singly infected with Pc; when Pc was followed by Sm, Co mice had fewer parasitized erythrocytes than Pc only infected mice

(*continued*)

TABLE 1.2 (*continued*)

Entry number	Reference	Species of trematode	Species of coinfecting organism	Experimental (E) or natural (N) infections in vertebrate hosts	Time between coinfections	Comments
30	Lewinsohn (1975)	*S. mansoni*	*P. berghei*	(E) Swiss mice	Sm followed by infection with Pb 3 or 5 wk later	Co mice had comparable levels of parasitaemia and reticulocytosis compared to mice singly infected with Pb
31	Moore et al. (1975)	*S. mansoni*	*P. berghei*	(E) mice (unknown)	Sm followed by Pb 6 wk later	Pigments from Sm and Pb in endothelial cells were very distinguishable after coinfection, though most cells tended to contain only one pigment type
32	Abdel-Wahab et al. (1974)	*S. mansoni*	*P. berghei*	(E) Swiss albino mice	Concurrently infected with Sm and Pb	Co mice had suppressed granuloma formation of Sm eggs in the lungs compared to singly infected mice; effect observed by day 4 and peaked at day 16; no differences observed in antibody levels between coinfected and mice singly infected with Sm

Co, coinfected; CM, cerebral malaria; Pb, *P. berghei*; Pc, *P. chabaudi*; Pf, *P. falciparum*; Pm, *P. malariae*; Py, *P. yoelii*; Sm, *S. mansoni*; Sh, *S. haematobium*; unknown, not specified in original paper; wk, week or weeks.

Plasmodium species, *P. falciparum*, *P. malariae* and *P. chabaudi*, infect humans. The remaining two malaria species, *P. berghei* and *P. yoelii*, are causative agents of murine malaria and were used in the mouse studies in addition to *P. chabaudi*. No papers were found on other species of *Schistosoma* or *Plasmodium* such as *S. japonicum* or *P. vivax* as coinfective agents.

1.2.1. Animal studies

All experimental studies were conducted on mice and used *S. mansoni*, and all but two experimental studies (entry numbers 29, 32) examined a species of *Schistosoma* followed by coinfection with a *Plasmodium* species. Typically, mice with a single *Plasmodium* infection served as controls. Overall, the differences in the effect of the coinfection on the host appeared to depend upon the species of *Plasmodium*, location of the malarial infection within the host and strain of mouse used.

The five studies using *P. chabaudi* infections were done on either C57 or CBA mice. In the two studies using C57 mice (entry numbers 24, 25), coinfection clearly increased the malaria parasitaemia and mortality of the host. In the three studies using CBA mice (entry numbers 26, 28, 29), parasitaemia was decreased in the host. Two of six studies using *P. berghei* (entry numbers 11, 18) showed that the interaction increased malaria parasitaemia and mortality when a patent or chronic infection of *S. mansoni* was followed by *P. berghei*. In one study (entry number 30), the author concluded that there was no effect of the coinfection, but examination of the data presented in the author's tables indicated that the coinfected hosts ended the experiment with increased splenomegaly and decreased haemoglobin levels compared to the mice infected singly with *Plasmodium*. Alternatively, two studies noted that coinfected mice had reduced severity of cerebral malaria (entry numbers 1, 5) (see Fig. 1.1, from Bucher et al., 2011), both of which followed patent infection with *S. mansoni*. This protective effect did not prevent severe disease or death (entry number 1) from other aspects of malaria in the coinfected animals and appeared to be correlated with a Th2 response (entry number 5).

In accord with some of the findings on *P. berghei*, results from work on *P. yoelii* (entry numbers 8, 28) found that coinfection increased parasitaemia and mortality in the experimental hosts. An increase in spleen size was also observed (entry number 8). A variety of mouse strains were used in the *S. mansoni–P. berghei* studies and also in the *S. mansoni–P. yoelii* studies, and no clear patterns in terms of possible interactions with the hosts were apparent. Interestingly, the only study (entry number 28) that found no effect on the host from a *S. mansoni–P. berghei* coinfection used a CBA mouse strain as the host, though the same study found an effect with a *S. mansoni–P. yoelii* interaction using the same CBA mouse strain. Two studies showed that there was no effect on the host in regard to

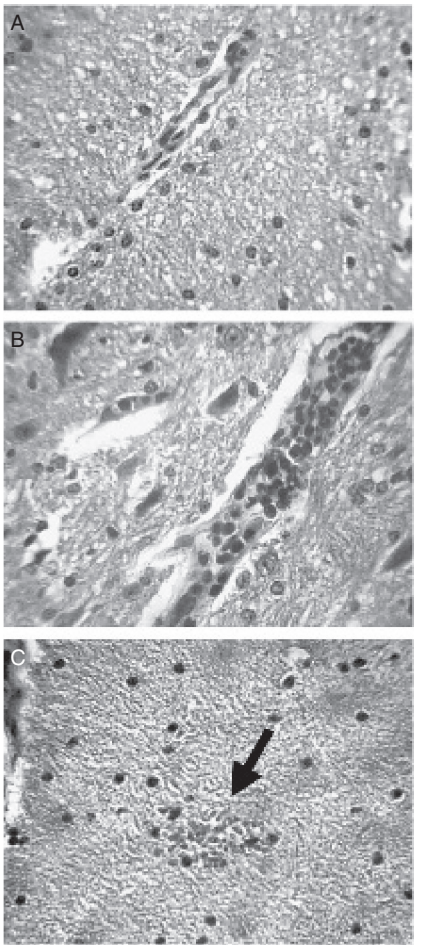

FIGURE 1.1 Histomorphology of brain sections of *Plasmodium berghei* ANKA-infected C57BL/6 mice on day 6 after challenge. (A) Brain section of a *Schistosoma mansoni–P. berghei* coinfected mouse showing a healthy uninfected blood vessel. (B and C) Brain sections of a *P. berghei* mono-infected animal showing (B) mononuclear cell accumulation and sequestration and (C) a microhaemorrhage (arrow). Sections stained with H&E. Magnification, 400×. Reproduced with permission from Bucher et al. (2011).

parasitaemia or cerebral malaria when coinfection with *P. chabaudi*, *P. berghei* or *P. yoelii* occurred following a pre-patent *S. mansoni* infection (entry numbers 5, 28). One study (entry number 26) indicated a delayed antibody response and higher parasitaemia in mice coinfected with *P. chabaudi* following pre-patent *S. mansoni* infection when compared with mice coinfected with *P. chabaudi* following a patent *S. mansoni* infection,

though parasitaemia levels in the coinfected hosts were still lower than in mice with single *Plasmodium* infection (entry number 26).

Several papers concluded that timing (entry numbers 5, 8, 26) with respect to the establishment of the *S. mansoni* infection as well as the malaria parasite load (entry number 5) was important. When infection with *S. mansoni* followed *P. chabaudi* in CBA mice (entry number 29), a decrease in parasitaemia was found. One study (entry number 32) examined mice concurrently infected with *P. berghei* and *S. mansoni* and found that coinfected hosts had suppressed granuloma formation in the lungs compared to mice with a single *S. mansoni* infection.

1.2.2. Human studies

All studies that examined naturally occurring coinfection in humans indicated that coinfection with schistosome and malaria organisms has an effect on the host, both in terms of pathology and in terms of immunological response. The direction of this response seems to depend on the species of schistosome and the worm burden, host age and malaria parasitaemia. Little can be inferred based on the order of coinfection since such information was unknown in all but one study (entry number 13). Eight papers examined the cytokine response with *P. falciparum* coinfection: five with *S. haematobium* (entry numbers 2, 7, 13, 17, 23) and three with *S. mansoni* (entry numbers 6, 9, 20). All but two (entry numbers 17, 21) of these studies were done on children 19 years or younger, with most children under 15 years of age.

All but 1 (entry number 22) of the 10 studies on *S. haematobium* in humans (entry numbers 2, 7, 13–17, 22, 23, 27) examined the effect of coinfection with *P. falciparum*. Studies that examined the pathological effects on the host found that coinfected hosts had decreased parasitaemia, deferred time to malaria attacks or decreased severity, and higher haemoglobin counts than those without an underlying *S. haematobium* infection (entry numbers 7, 14–16, 22). One study noted that the effect was only found in young children (entry number 16) or those children with a relatively light worm burden (entry number 15). Though the malaria species was not identified, decreased splenomegaly was also observed in coinfected humans in another study (entry number 22). Five of the *S. haematobium–P. falciparum* studies examined immunological effects (entry numbers 2, 7, 13, 16, 17). Three of these studies noted an age effect on the immune response, with young children (typically between 4 and 8 years old) showing different patterns than older children in their cytokine responses (entry numbers 13, 16, 17). Overall, the studies indicated that coinfection with *S. haematobium* probably mediated the incidence and severity of infection with *P. falciparum* (entry numbers 7, 13–17, 22), possibly in an age-dependent manner (entry numbers 13, 16, 17).

Five of 19 human studies examined the effects of *S. mansoni* coinfection with *P. falciparum* (entry numbers 6, 9, 10, 19, 20). One additional study used an undetermined species of *Plasmodium* (entry number 21). All studies with *S. mansoni* found a detrimental effect of the coinfection on the host, with increased malaria attacks (entry numbers 10, 19) or increased host hepatomegaly and splenomegaly (entry numbers 9, 20, 21). An age effect was also observed in one study (entry number 10), in which children under the age of five had higher levels of parasitaemia than older children. Increased egg load of *S. mansoni* was also associated with increased malaria attacks, but not in a simple linear relationship (entry number 19). Aspects of the cytokine response were examined in two studies, which concluded that lower T lymphocyte subsets may be related to differential morbidity or the course of infection (entry number 6) and higher levels of IL10, IL12p70, IL 13 and sTNFR11 may be associated with inflammatory responses in the liver and spleen (entry number 9).

The remaining studies examined *S. mansoni* and *S. haematobium* coinfections with *P. falciparum* (entry numbers 3, 4) or failed to identify the species of *Schistosoma* or *Plasmodium* (entry number 12) used. These studies showed similar results to the *S. mansoni–P. falciparum* findings noted above, with coinfected hosts experiencing increased anaemia and parasitaemia. Several reviews discussed immunological and pathological aspects of helminth interactions with *Plasmodium* (e.g. Brooker et al., 2007; Hartgers and Yazdanbakhsh, 2006; Helmby, 2007; Nacher, 2008). Some prevalence studies and case reports documented this coinfection in children (e.g. Mazigo et al., 2010; Midzi et al., 2008), particularly the exacerbation of hepatosplenomegaly when coinfected with *S. mansoni* and *Plasmodium* (e.g. Wilson et al., 2007, 2010).

1.3. COINFECTION OF *SCHISTOSOMA* SPECIES WITH PROTOZOANS OTHER THAN IN THE GENUS *PLASMODIUM*

This section covers coinfection with species of *Schistosoma* and protozoans other than those in the genus *Plasmodium*. Twenty nine studies were included in Table 1.3; they examined coinfection between species of *Schistosoma* and four protozoans other than *Plasmodium*. The studies examined were *Leishmania* (entry numbers 1–9), *Toxoplasma* (entry numbers 10–18), *Entamoeba* (entry numbers 19–25) and *Trypanosoma* (entry numbers 26–29). Although most studies involved *S. mansoni* (entry numbers 1–20, 22–29), two also examined *S. haematobium* (entry number 11) and *S. japonicum* (entry number 21), and one examined *S. bovis* (entry number 27), a non-human form. The coinfection pairs are arranged in the table in the order listed above and discussed in the following sections.

TABLE 1.3 Coinfection studies of *Schistosoma* species and protozoans other than *Plasmodium*

Entry number	Reference	Species of trematode	Species of coinfecting organism	Experimental (E) or natural (N) infections in vertebrate hosts	Time between coinfections	Comments
Leishmania						
1	Hassan et al. (2006)	*Schistosoma mansoni*	*Leishmania donovani*	(E) C57BL/6 mice	Sm followed by Ld 8 wk later	Co mice had similar Sm parasite burden and egg-induced granulomatous response than mice with single Sm infections; Co mice had greater Ld parasite burden in liver and spleen than mice with single Ld infections, despite delayed but functional anti-Ld Th1 response; granulomatous tissue responses to Sm formed a discrete niche facilitating survival of intracellular Ld pathogens
2	La Flamme et al. (2002)	*S. mansoni*	*L. major*	(E) C57BL/6 mice	Sm followed by Lm 2 wk later	Pre-infection with Sm delayed the development and resolution of Lm lesions; Lm infection had no impact on the course of Sm infection in coinfected mice; pre-establishment of a strong Th2 response can modulate Th1 cytokine responses and result in exacerbation of Th1-controlled infections
3	Yoshida et al. (1999)	*S. mansoni*	*L. major*	(E) BALB/c and C57BL/6 mice	Sm followed by Lm 8 wk later	Despite any differences between groups during course of infection, after 6 wk of infection Co mice had comparable footpad thickness to mice with single Ld infection; footpad thickness was greater in Lm susceptible BALB/c mice than Lm resistant C57BL/c mice
4	Mangoud et al. (1998a)	*S. mansoni*	*L. d. infantum*	(E): Syrian golden hamster	Sm followed by Ldi 4 wk later	Renal changes in Co hosts were comparable to animals with either single infection, but infection due to Ldi occurred earlier and were more obvious; Ldi may have modified the severity of previous infection with Sm

(*continued*)

TABLE 1.3 (*continued*)

Entry number	Reference	Species of trematode	Species of coinfecting organism	Experimental (E) or natural (N) infections in vertebrate hosts	Time between coinfections	Comments
5	Mangoud et al. (1998c)	*S. mansoni*	*L. d. infantum*	(E) Syrian golden hamster	Sm followed by Ld 4 wk later	Sm granulomas were smaller and less frequent in Co hamsters compared to Sm-infected controls; Ldi caused early appearance of cell necrosis and fatty change; Ldi infection on top of Sm suppressed Sm infection and accelerated fibrosis, while infection due to Ldi became more pronounced
6	Mangoud et al. (1998b)	*S. mansoni*	*L. d. infantum*	(E) hamster	Sm followed by Ld 4 wk later	Heart and lungs of Co hosts presented leishmanial cardiac granulomas at 12 wk; pulmonary granulomas appeared earlier in Co hosts than in controls
7	Morsy et al. (1998)	*S. mansoni*	*L. d. infantum*	(E) Syrian hamster	Sm followed by Ldi 4 wk later	Co hamsters had delayed appearance of Sm and Ldi granulomas in small intestine compared to controls with either single infection
8	Mangoud et al. (1997)	*S. mansoni*	*L. d. infantum*	(E) Syrian golden hamster	Sm followed by Ldi 4 wk later	Co hamsters had greater IgG, IgA, IgE responses and greater decrease in C3 and C4 than animals with either single infection
9	Coelho et al. (1980)	*S. mansoni*	*L. mexicana mexicana*	(E) mice, type not specified	Sm followed by Lmm 60 days later	Lmm lesions appeared in all Co mice, but in only one Lmm control animal; incubation period for Lmm was shorter in animals with underlying Sm infection

Toxoplasma

10	Araujo et al. (2001)	*S. mansoni*	*Toxoplasma gondii*	(E) C57BL/6 B6 and Swiss-Webster B6 Interleukin (IL) 12(−/−) mice	Sm followed by Tg 7 wk later	Co IL-12-deficient mice had decreased liver damage, prolonged time to death and higher levels of Tg in their livers compared to controls; production of inflammatory mediators was defective in IL-12-deficient animals; IL-12 promoted liver damage during coinfection
11	Afifi et al. (2000)	*S. haematobium* or *S. mansoni*	*T. gondii*	(N) humans, age not specified	Unknown	Levels of soluble intracellular adhesion molecule 1 (sICAM-1) were correlated with disease severity and pathogenesis; Co patients had higher levels of SICAM-1 molecule compared to either single infection; response in Co humans was similar to infection with hepatosplenic Sm, indicating a weak Th1 response in Co patients
12	Marshall et al. (1999)	*S. mansoni*	*T. gondii*	(E) C57BL/6 mice	Sm followed by Tg 7 wk later	Co mice had increased morbidity and mortality compared to mice with Tg alone; moribund Co mice displayed severe liver disease including steatosis and coagulative necrosis in areas adjacent to egg granulomas; prior infection with Sm increased sensitivity to Tg infection
13	Hammouda et al. (1994a)	*S. mansoni*	*T. gondii*	(E) Swiss albino mice	Tg followed by Sm 1 wk to 2 months later	Co mice had increased spleen weights but no difference in mean liver weights compared to mice with single Sm infection; Co mice had lower Sm worm loads than other groups; prior infection with Tg increased resistance to Sm
14	Hammouda et al. (1994b)	*S. mansoni*	*T. gondii*	(E): Swiss albino mice	Tg followed by Sm 1 wk to 2 months later	Co mice had increased B-lymphocytes, decreased levels of anti-Sm antibodies and cellular immune responses, and reduced granuloma size compared with single Sm-infected controls; toxoplasmosis induced humoural and cellular immunosuppression to Sm

(*continued*)

TABLE 1.3 (*continued*)

Entry number	Reference	Species of trematode	Species of coinfecting organism	Experimental (E) or natural (N) infections in vertebrate hosts	Time between coinfections	Comments
15	Fayad et al. (1992)	*S. mansoni*	*T. gondii*	(N): Human, ages not specified	Unknown	Progression of liver disease in Co patients with Sm and latent Tg infection comparable to patients with liver disease from single Sm infection
16	Kloetzel et al. (1977)	*S. mansoni*	*T. gondii*	(E) Albino mice	Sm followed by Tg 59 days later; Tg followed by Sm 47 days later	Mice infected with Sm followed by Tg had massive mortality during the acute stage of infection, great weight loss and pronounced splenomegaly compared with controls; relatively few notable effects when Tg preceded Sm
17	Mahmoud et al. (1977)	*S. mansoni*	*T. gondii*	(E) Swiss albino mice	Sm followed by Tg 4 wk later; Tg followed by Sm 1 day or 4 wk later	Co hosts had smaller hepatic granulomas and lower mean portal pressure compared to mice with single Sm infection; compared to other timing and order sequences, mice infected with Sm followed by Tg 4 wk later had increased spleen weight; mice infected with Tg 1 day before Sm had reduced body weight and greatly increased mortality
18	Mahmoud et al. (1976)	*S. mansoni*	*T. gondii*	(E) Swiss albino mice	Sm followed by Tg 4 wk later; Tg followed by Sm 1 day or 4 wk later	Mice infected with Sm followed by Tg at 4 wk had similar worm burdens and mean liver egg counts compared to controls; mice infected with Tg followed by Sm at 1 day or 4 wk had reduced worm burdens and liver egg counts (43% and 35%, respectively) compared with controls

Entamoeba						
19	Dolabella et al. (2007)	*S. mansoni*	*Entamoeba histolytica*	(E) Syrian hamsters	Sm followed by Eh 70 days later	Co hosts had increased morbidity and mortality compared to animals with either single infection; adhesion of Eh trophozoites on Sm granulomas not observed in histological sections, but Co hosts displayed severe wasting and greater number of amoebic lesions in livers; Sh aggravated the course of the Eh infection
20	Mansour et al. (1997)	*S. mansoni*	*E. histolytica*	(N) Human, ages not specified	Unknown	Prevalence of Eh was higher in the Sm endemic village compared to the non-Sm village; detection of Eh was higher by stool samples than serologic tests; Sm may suppress immune response of the host and increase susceptibility to Eh infection
21	Liu et al. (1991)	*S. japonicum*	*E. histolytica*	(E) Mongolian gerbil	Concurrently infected with Sj and Eh	Sj promoted caecal amoebiasis and stimulated symbiotic Eh infection to invasive caecal amoebiasis; trophozoites of Eh adhered to egg shell of Sj at tissue necrosis site; affinity between trophozoites of Eh and ova of Sj was noted
22	Abo-Shady and Yossef (1986)	*S. mansoni*	*E. histolytica*	(N) 24- to 56-year-old humans	Unknown	Eh coinfected 47.8% of patients with Sm colonic polypsis; 29.9% of patients with simple colonic Sm lesions; 11.9% of non-Sm-infected controls; severity of colonic Sm lesions directly correlated with higher prevalence and level of invasiveness of hematophagous trophozoites due to Eh coinfection
23	Ali et al. (1984)	*S. mansoni*	*E. histolytica*	(N) 3- to 64-year-old humans	Unknown	Patients with Sm infection had higher Eh coinfection (53.32%) than non-Sm-infected patients (13.78%); damage by Sm ova in intestinal mucosa may have promoted proliferation and invasion of Eh into mucosa

(*continued*)

TABLE 1.3 (*continued*)

Entry number	Reference	Species of trematode	Species of coinfecting organism	Experimental (E) or natural (N) infections in vertebrate hosts	Time between coinfections	Comments
24	El Raziky et al. (1983)	*S. mansoni*	*E. histolytica*	(N) 13- to 50-year-old humans	Unknown	Eh coinfected 37% of the patients with Sm colonic polypsis; 15% of the patients with Sm without polypsis; 11% of the patients without Sm infection; high correlation between colonic polypsis and amaeobiasis noted
25	Knight and Warren (1973)	*S. mansoni*	*E. histolytica*	(E) Swiss albino mice	Sm followed by Eh 5–13 wk later	Coinfection increased the infectivity of the Eh inoculum and the subsequent amoebic tissue invasion; some correlation existed with the worm load; infectivity of Eh strain matters
Trypanosoma						
26	Fagbemi (1987)	*S. mansoni*	*Trypanosoma brucei*	(E) albino mice	Sm followed by Tb 2 wk later; Sm followed by Sm challenge 6 wk later	Co mice had a lower faecal egg count per worm pair in faeces and small intestines compared to mice with single Sm infections; infection with Tb may suppress immune response to Sm
27	Fagbemi et al. (1987)	*S. mansoni*, *S. bovis*	*T. brucei*	(E) albino mice	Tb followed by Sm or Sb 7 days later	Co mice had a lower frequency of granulomatous response and reduced diameter of granuloma compared to mice with single Sm or Sb infection; a similar response was obtained with Sm or Sb; Tb infection had an immunosuppressive effect on the host infections with Sm or Sb

28	Genaro et al. (1986)	*S. mansoni*	*T. cruzi*	(E) Swiss albino mice	Sm followed by Tc 43 days later; Tc followed by Sm 68 and 185 days later	When Sm followed by Tc, Co had 49% reduction in diameter of hepatic granuloma size compared to Sm controls; when Tc was followed by Sm 68 and 185 days later, Co had 47% and 37% reduction (respectively) in diameter of hepatic granulomas compared to Sm controls; Tc depresses Sm granuloma size, delaying hypersensitive immune response during acute and chronic phase of Tc infection
29	Kloetzel et al. (1973)	*S. mansoni*	*T. cruzi*	(E) albino mice	Sm followed by Tc 66 days later; Tc followed by Sm 4 to 63 days later	Coinfection enhanced Tc parasitaemia in all experiments; when Sm preceded Tc, Co mice had increased splenomegaly and higher mortality compared with controls; longer duration of parasitaemia noted in Co mice that had been exposed percutaneously but not subcutaneously infected with Sm; when Tc preceded Sm, Co mice had higher average peaks than controls

Co, coinfected; Eh, *E. histolytica*; Ld, *L. donovani*; Lm, *L. major*; Ldi, *L. donovani infantum*; Lmm, *L. mexicana mexicana*; Sm, *S. mansoni*; Sb, *S. bovis*; Tc, *T. cruzi*; Tg, *T. gondii*; Tb, *T. brucei*; unknown, not specified in original paper; wk, week or weeks.

1.3.1. *Leishmania*

All studies *on Schistosoma–Leishmania* coinfections (entry numbers 1–9) were experimental studies on mice (entry numbers 1–3, 9) or hamsters (entry numbers 4–8) and examined a schistosome infection followed by coinfection with *Leishmania*. Three species of *Leishmania* were used: two with *L. major* (entry numbers 2, 3), one with *L. mexicana* (entry number 9), and six with *L. donovani* (entry numbers 1, 4–8). The studies differed in that they examined 2- (entry number 2), 4- (entry numbers 4–8), or 8-week (entry numbers 1, 3, 9) intervals between coinfections.

In most studies, prior infection with *S. mansoni* allowed the subsequent coinfection with *Leishmania* to develop earlier, become more pronounced, or persist longer than in hosts with single *Leishmania* infection (entry numbers 1, 2, 4–6, 9). These effects appeared to depend on the interval between coinfection. The greatest pathological effects occurred when *Leishmania* coinfection followed a patent schistosome infection, increasing the parasite burden from *L. donovani* in both the liver and the spleen (entry number 1); changes were also observed in the liver, lungs and heart when coinfection occurred after a 4-week interval (entry numbers 5, 6). One study hypothesized that the granuloma response by *S. mansoni* formed a discrete niche that facilitated the intracellular survival of *Leishmania* organisms (entry number 1). Another study proposed that the effect was due to the early establishment of a strong Th2 cytokine response by prior infection with *S. mansoni*, which modulated the later Th1-based response to *Leishmania* (entry number 2). There have been a few case reports of this coinfection in human populations in China and East Africa that appear to support either of these findings, where coinfection with helminths delayed the resolution of leishmaniasis (Muigai et al., 1989; O'Neal et al., 2007).

Similarly, the effect of *Leishmania* on an underlying infection with *Schistosoma* may also depend upon the interval between coinfection. There was no observed effect on the course of the *Schistosoma* infection when *S. mansoni* was followed by *Leishmania* at 2- or 8-week intervals (entry numbers 2, 1, respectively), but the severity of the schistosome infection was reduced when *Leishmania* followed *Schistosoma* by 4 weeks (entry numbers 4, 5). The host species may have played a role in this since both the 2- and 8-week studies were done on mice and the 4-week studies on hamsters. In addition, most of the mice studies used the C57 strain (entry numbers 1–3) which was found to be more resistant to *Leishmania* than the Balb/C strain (entry number 3).

1.3.2. *Toxoplasma*

The nine studies in this section examined coinfection of *S. mansoni* with *Toxoplasma gondii*. One study also included *S. haematobium*, in addition to *S. mansoni* (entry number 11). Seven studies were done on mice (entry

numbers 10, 12–14, 16–18) and examined the effect of infection with *S. mansoni* followed by coinfection with *T. gondii* (entry numbers 10, 12, 16–18) as well as infection with *T. gondii* followed by coinfection with *S. mansoni* (entry numbers 13, 14, 16–18). There were also two studies on humans, and in both, the order and timing of the coinfection were not reported (entry numbers 11, 15).

1.3.2.1. Animal studies

Overall, two distinct patterns were noted: coinfection that followed a patent *S. mansoni* infection appeared to increase the sensitivity or severity to subsequent infection with *T. gondii* (entry numbers 12, 16), while infection with *T. gondii* modulated or decreased the severity of the subsequent infection with *S. mansoni* (entry numbers 13, 14, 17, 18). All studies used either C57 or Swiss albino mice, and no strain effect was apparent. Studies on infection with *S. mansoni* followed by *T. gondii* examined the coinfection effect of *T. gondii* at 4- (entry numbers 17, 18), 7- (entry numbers 10, 12) or 8-week (entry number 16) intervals. The most consistent findings were noted at 7- and 8-week intervals, at which time coinfected mice showed greater mortality, more severe liver damage, greater weight loss and increased splenomegaly than mice with a single *T. gondii* infection (entry numbers 12, 16). This effect was particularly noted during the acute stage of toxoplasmosis (entry numbers 12, 16). One study that examined the role of inflammatory mediators found that IL-12 contributed to the increased liver damage observed in coinfected hosts (entry number 10). Mice coinfected with *T. gondii* at 4-week intervals had increased spleen weight in one study (entry number 17) but not in another (entry number 18).

Studies on *T. gondii* followed by *S. mansoni* examined worm pairing at 1- to 28- (entry numbers 17, 18), 47- (entry number 16), or 7- to 56-day intervals (entry numbers 13, 14). Most studies noted that coinfected hosts had reduced worm burdens and liver egg counts, smaller granulomas and decreased levels of *S. mansoni* antibodies than mice with single *S. mansoni* infections (entry numbers 13, 14, 17, 18). An exception was noted when mice were infected with *T. gondii* followed by *S. mansoni* 1 day later, which resulted in higher mortality and a reduced body weight in coinfected hosts (entry number 17). Few effects of coinfection were noted in the one study that used a 47-day interval (entry number 16).

1.3.2.2. Human studies

Two studies were done on humans (entry numbers 11, 15). The timing and order of infection in these studies were unknown, but results showed similarities to the findings observed in the previous animal studies. One study found that coinfected patients had higher levels of an immune substance that was correlated with disease severity and pathology than

in humans with either single infection (entry number 11). This study also noted that responses of coinfected subjects were similar to patients with hepatosplenic *S. mansoni* and may have indicated a weakened Th1 response (entry number 11). This finding is in accord with the effect observed in mice that were coinfected with *T. gondii* following a patent *S. mansoni* infection (entry numbers 12, 16). The other study found that the progression of liver disease in coinfected patients was comparable to that seen in single *S. mansoni* infections (entry number 15), which is similar to the effect observed when *S. mansoni* infection preceded *T. gondii* by 4 weeks (entry number 18).

1.3.3. *Entamoeba*

Seven studies examined the effect of coinfection of *Schistosoma* and *Entamoeba*: of these, three were done on animals (entry numbers 19, 21, 25) and four on humans (entry numbers 20, 22–24). Most studies (entry numbers 19, 20, 22–25) examined *S. mansoni* and *E. histolytica* coinfections. One study done in China examined coinfection of *S. Japonicum* and *E. histolytica* (entry number 21).

1.3.3.1. Animal studies

The three studies done on animals each used rodent hosts (entry numbers 19, 21, 25). Two examined an infection with *S. mansoni* followed by *E. histolytica* at 10 weeks in the hamster (entry number 19) and 5–13 weeks in albino mice (entry number 25). In both cases, prior infection with *S. mansoni* increased the subsequent infection with *E. histolytica*, increased amoebic tissue invasion, mortality and caused severe wasting compared to animals with a single *E. histolytica* infection. The same effect was noted when the Mongolian gerbil was simultaneously infected with *S. japonicum* and *E. histolytica*, which stimulated invasive caecal amoebiasis (entry number 21). This paper suggested an affinity between the trophozoites of *E. histolytica* and the eggs of *S. japonicum* that may serve to stimulate *E. histolytica* infection to produce invasive amoebiasis (entry number 21).

1.3.3.2. Human studies

The four human studies (entry numbers 20, 22–24) were done on subjects ranging in age from 3 to 64 years, and the order and timing of infection were unknown. The results were similar to those of the animal studies noted above, in that patients with *S. mansoni* had higher levels of coinfection with *E. histolytica*. The severity of *S. mansoni* colonic polypsis was directly associated with increased levels of *E. histolytica* infection with amoebic invasiveness (entry numbers 22–24). One study hypothesized that damage by *S. mansoni* eggs in the intestinal mucosa may promote

the proliferation and invasion of *E. histolytica* into the mucosa (entry number 23), whereas another suggested that infection with *S. mansoni* may suppress the immune response and increase susceptibility to *E. histolytica* (entry number 20). For further discussion of immunological aspects of coinfection with *S. haematobium*, *E. histolytica* and other organisms in children, see Hamm et al. (2009).

1.3.4. *Trypanosoma*

Four studies were done on coinfection of *Trypanosoma* and *Schistosoma* (entry numbers 26–29); all were done in albino mice. *S. mansoni* was used in all studies and one study also included *S. bovis* (entry number 27). Two species of *Trypanosoma* were studied, *T. brucei* (entry numbers 26, 27) and *T. cruzi* (entry numbers 28, 29), both of which infect humans and animals. Two studies examined the effect of the coinfection when *Schistosoma* preceded *Trypanosoma* as well as when *Trypanosoma* preceded *Schistosoma* (entry numbers 28, 29). Three of the four studies suggested that infection with *T. cruzi* or *T. brucei* suppressed coinfection with *S. mansoni* or *S. bovis* regardless of the order of infection (entry numbers 26, 27, 28).

Three studies examined infection with *S. mansoni* followed by *T. brucei* 2 weeks later (entry number 26) or *T. cruzi* 43 days later (entry number 28) or *T. cruzi* 66 days later (entry number 29). In the first two studies, the coinfected hosts had smaller hepatic granulomas and decreased egg counts and worm burdens compared to those with single *S. mansoni* infections (entry numbers 26, 28). The last study, which examined the longest interval between coinfections, showed contrary results. In this study, coinfected mice had increased splenomegaly and higher mortality compared with controls, as well as a higher *T. cruzi* parasitaemia (entry number 29).

Three studies also examined the effects of a prior *Trypanosoma* infection followed by an infection with *Schistosoma*. In the first study, *T. brucei* was followed by *S. mansoni* or *S. bovis* at 7 days (entry number 27); in the second study, *T. cruzi* was followed by *S. mansoni* at 68 and 185 days (entry number 28); and in the last study, *T. cruzi* was followed by *S. mansoni* 4–63 days later (entry number 29). The first two studies found that coinfected mice had smaller hepatic granulomas than mice with single *Schistosoma* infection (entry numbers 27, 28). No differences in response based on *S. mansoni* or *S. bovis* were observed, though the protective effect appeared to have weakened with increased time between coinfection (entry number 28). The third study focused on the effect of the *T. cruzi* infection and found higher average peak parasitaemia in the coinfected hosts when compared to mice with a single *T. cruzi* infection; the duration of the infection was longer in mice infected percutaneously than mice infected subcutaneously (entry number 29).

1.4. COINFECTION OF *SCHISTOSOMA* SPECIES WITH *SALMONELLA*

A total of 16 studies were included in Table 1.4, which covers the interactions between four species of *Schistosoma* and a number of *Salmonella enterica* serotypes or subspecies. The four species of *Schistosoma* are *S. mansoni*, *S. haematobium*, *S. intercalatum* and *S. japonicum*. Both typhoidal (serotypes Typhi and Paratyphi A, B or C) and non-typhoidal (other serotypes including Typhimurium, Enteritidis and subspecies *arizonae*) *Salmonella* were included. In addition, a few studies compared strains of *Salmonella* that were piliated, that is, bacteria with hair-like surface appendages known as pili, along with non-piliated forms (entry numbers 7–9). Pili occur on some bacteria and may have increased the ability of the bacteria to attach to and colonize in a host; the piliated types have been associated with increased virulence (Engelkirk et al., 2011).

1.4.1. Animal studies

Ten of 16 studies in this section were animal experiments: eight were done on various types of mice (entry numbers 2, 6–9, 12, 15, 16) and two on the Syrian Golden Hamster (entry numbers 13, 14). Most animal studies were consistent in finding that a prior *Schistosoma* infection enhanced and prolonged a subsequent infection with *Salmonella*. In particular, coinfected hosts had greater bacteremia, increased virulence, higher mortality and more persistent local infection in the liver or spleen compared with hosts with single *Salmonella* infection (entry numbers 2, 6–8, 12–16). Several interesting details were highlighted in these studies. The effect of the coinfection was greatest when the *Salmonella* infection followed a 6- or 8-week *Schistosoma* infection (entry numbers 2, 7, 8, 14) and also when *Salmonella* was introduced into the host by the oral route rather than intravenously (entry number 16). Although piliated strains of bacteria were often associated with higher virulence, in these studies, both the piliated and non-piliated strains were equally virulent in coinfected hosts (entry numbers 7–9). One study also reported the effect of the coinfection on *Schistosoma* and found that coinfected hosts had a greater hepatic worm burden than hosts with a single *Schistosoma* infection (entry number 13).

Several studies reported that *Salmonella* bacteria multiplied in and adhered to the schistosome worms, suggesting that these worms may be the vehicle through which the infectivity of *Salmonella* is enhanced and prolonged (entry numbers 9, 13, 15). In particular, adult female schistosomes were identified as being more frequently positive than males in harbouring *Salmonella* (entry numbers 9, 13). Coinfected hosts were also

TABLE 1.4 Coinfection studies with *Schistosoma* and *Salmonella*

Entry number	Reference	Species of trematode	Species of coinfecting organism[a]	Experimental (E) or natural (N) infection in vertebrate hosts	Time between coinfections	Comments
1	Nwaugo et al. (2005)	*S. haematobium*	Unidentified *Salmonella* sp.	(N) humans, mainly <51 years of age	Unknown	Patients with Sm infection were more likely to have concurrent typhoid fever than patients without Sm infection (46–51% vs. 10%); individuals aged 10–30 years had higher infection rates than older patients; males and female subjects were equally coinfected
2	Njunda and Oyerinde (1996)	*S. mansoni*	*S.* Typhi	(E) albino mice	Sm followed by ST at 2, 4 or 8 wk	Co mice infected with ST 8 wk after Sm infection had greater bacteremia, more persistent local infections in internal organs and higher mortality than mice infected with ST at 2 or 4 wk post-Sm or than mice with single ST infection; adult male schistosomes harboured more ST bacteria than adult females; Sm enhanced the bacterial virulence of ST
3	Abdul-Fattah et al. (1995)	*S. mansoni*	*S.* Typhi	(N) humans, age not specified	Unknown	Glomerulopathy in coinfected subjects was mainly due to ST infection; Sm had a minor additive effect on the coinfected patients; once hepatic fibrosis was established, glomeruli development appeared to be affected by circulating immune complexes from either infection

(*continued*)

TABLE 1.4 (*continued*)

Entry number	Reference	Species of trematode	Species of coinfecting organism[a]	Experimental (E) or natural (N) infection in vertebrate hosts	Time between coinfections	Comments
4	Gendrel et al. (1994)	*S. intercalatum*	*S.* Typhimurium, *S.* Enteritidid, *S. galiema*, *S. arizonae*, *S.* Typhi, *S.* Paratyphi	(N) 2- to 16-year-old humans	Unknown	Children with Si and non-typhoidal salmonellosis had symptoms of septicemia comparable to children with single ST infection; prolonged fever (up to 26 days), swollen spleen and severe diarrhoea were noted; underlying infection with Si interacted with non-typhoidal *Salmonella*
5	Martinelli et al. (1992)	*S. mansoni*	Various unidentified *Salmonella* species including *S.* Typhi	(N) humans (mean ages 18 and 23 years)	Unknown	Patients with hepatosplenic schistosomiasis and prolonged *Salmonella* bacteremia coinfection had comparable renal histopathological findings to patients with schistosomal glomerulonephritis without *Salmonella* infection; pronounced glomerular hypercellularity and interstitial mononuclear cell infiltration were noted in Co patients
6	Muniz-Junqueira et al. (1992)	*S. mansoni*	*S.* Typhimurium	(E) Charles River mice	Sm followed by STy 4–6 months later	Co mice had reduced phagocytosis and intracellular destruction of the bacteria compared to mice infected only with STy; underlying Sm infection altered the function of macrophages and may have played a role in the development of chronic salmonellosis

7	Tuazon et al. (1986)	*S. japonicum*	*S.* Enteritidis, *S.* Typhimurium (piliated and non-piliated)	(E) Swiss mice	Sm followed by SE or STy 6 wk later	Co mice showed more rapid mortality (100% in 24 h) than mice with single Sm infection (100% in 9–15 days) or mice with single *Salmonella* infection (piliated 75% to non-piliated 86% by day 15)
8	Tuazon et al. (1985a)	*S. mansoni*	*S.* Typhimurium (piliated and non-piliated)	(E) Swiss mice	Sm followed by STy 6 wk later	Co mice had greater mortality than mice with single STy or Sm infections; after 7 days, Co mice with piliated STy (81%) or non-piliated STy (73%) had higher mortality than mice with single Sm infection (no mortality) or single piliated STy (27%) or single non-piliated STy (4%) infections
9	Tuazon et al. (1985b)	*S. japonicum*	*S.* Typhimurium (piliated and non-piliated)	(E) Swiss mice	Sm followed by STy 6 wk later	Worms were harvested from mice 16–18 h after coinfection; female schistosomes were more frequently positive for STy than male schistosomes; non-piliated STy bacteria adhered to more female than male schistosomes; no difference observed in adherence of piliated STy bacteria
10	Carvalho et al. (1983)	*Schistosoma* sp.	*Salmonella* sp.	(N) 8- to 66-year-old humans	Unknown	Patients with schistosomiasis and chronic *Salmonella* bacteremia had higher circulating immune complexes than patients with schistosomiasis alone; Co patients had increased C1q-binding complex; mean c3 levels were lower in patients without renal involvement

(*continued*)

TABLE 1.4 (*continued*)

Entry number	Reference	Species of trematode	Species of coinfecting organism[a]	Experimental (E) or natural (N) infection in vertebrate hosts	Time between coinfections	Comments
11	Gendrel et al. (1984)	*S. intercalatum*	*S.* Typhi, *S.* Paratyphi strains *C*, *B*	(N) 3- to 18-year-old humans	Unknown	Co patients with typhoid or paratyphoid fever were more likely to relapse if underlying Si infection was not treated; Si prolonged the infection with *Salmonella* sp.
12	Bonfim de Lima et al. (1982)	*S. mansoni*	*S.* Typhimurium	(E) white mice	Sm and STy at same time; Sm followed by STy at 120 or 180 days	Mice coinfected at same time had much greater mortality than mice with single STy infection; mice coinfected at 120 days had slightly increased mortality than controls; mice coinfected at 180 days had mortality equivalent to controls
13	Mikhail et al. (1982)	*S. mansoni*	*S.* Paratyphi strain A	(E) Golden hamsters	Sm followed by SPa 6 wk later	Co hamsters had higher percentage of Sm worms in the hepatic veins than did hamsters with single Sm infection (83% vs. 48%); adult Sm worms were the major sites of SPa adherence and colonization and nutritional factors may have been involved; higher bacteria counts were also noted in the female worms
14	Mikhail et al. (1981)	*S. mansoni*	*S.* Paratyphi strain A	(E) Golden hamsters	Sm followed by SPa 6 wk later	Co hamsters had prolonged bacteremia, diffuse visceral involvement and higher mortality than hamsters with single SPa infection; Sm prolonged and enhanced SPa infection

15	Rocha et al. (1971)	*S. mansoni*	*S.* Typhi	(E) mice, strain not specified	Sm followed by ST 40–50 days later	Co mice retained ST bacteria in blood, liver and spleen longer than mice with single ST infections; ST bacteria multiplied within Sm worms in first week but were not present after 2 wk
16	Collins et al. (1972)	*S. mansoni*	*S.* Enteritidis	(E) CF-1 and CD-1 mice	Sm followed by SE 18 wk later	Mice coinfected with SE orally had higher levels of bacteria in the liver and spleen, and greater mortality than mice with single orally administered SE infection; mice coinfected with SE orally had more severe systemic infection than mice with SE administered intravenously; CF-1 mice were used for most experiments

[a] Co, coinfected; SE, *S.* Enteritidis; Sm, *S. mansoni*; Sh, *S. haematobium*; Si, *S. intercalatum*; Sj, *S. japonicum*; Spa, *S.* Paratyphi a; ST, *S.* Typhi; Sty, *S.* Typhimurium; unknown, not specified in original paper; wk, week or weeks.

found to have altered macrophage activity, which may have played a role in the development of chronic salmonellosis (entry numbers 7, 15, and Lambertucci et al., 1998). No other patterns seemed apparent between *Schistosoma* species and *Salmonella* serotypes, or by the type or strain of rodent most used in these studies.

1.4.2. Human studies

Four of the six studies done on humans appeared to be in agreement with the animal studies discussed above (entry numbers 1, 4, 10, 11). Two studies done on children infected with *S. intercalatum* found that coinfection prolonged the infection from *Salmonella* Typhi or Paratyphi, and that subjects who were coinfected with *Schistosoma* and non-typhoidal *Salmonella* strains had increased disease severity comparable to subjects with typhoidal forms of the disease (entry number 4) and prolonged disease (entry number 11). Similarly, a study examining *S. haematobium* found that the coinfection may have increased the risk of typhoid fever (entry number 1). Madbouly et al. (1993) reported that patients with *Schistosoma* were more likely to have concurrent infection with *Salmonella* than patients without schistosomes, and that tegumental tubercles (also known as bosses) infected with *Salmonella* bacteria were found in several coinfected hosts (see Fig. 1.2 from LoVerde et al., 1980). An extensive case report of patients in the Sudan provided additional clinical data on the coinfection, indicating that coinfected patients had prolonged fever, severe anaemia and hepatosplenic involvement (Salih et al., 1977). Other case reports provided similar findings and indicated that the *Salmonella* infection could not be resolved without treating the underlying *Schistosoma* infection (e.g. Botterel et al., 1996; Bourée et al., 2002; Friedland and Loubser, 1990; Gendrel et al., 1986; Lambertucci et al., 1987, 1988).

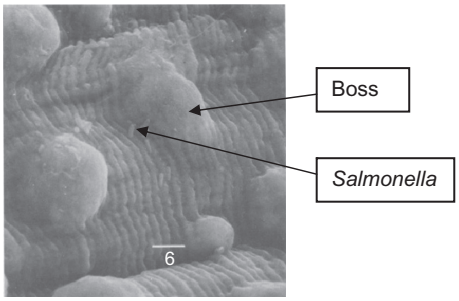

FIGURE 1.2 Scanning electron micrograph of the interaction of *Salmonella* Typhimurium LT2 and *Schistosoma mansoni*, Puerto Rice, showing salmonellae associated with a tegumental boss (1600×). Bar units = μm. Reproduced with permission from LoVerde et al. (1980).

Several studies have examined the surface interactions between species of *Schistosoma* and *Salmonella* (e.g. LoVerde et al., 1980; Melhem and LoVerde, 1984; Miegeville et al., 1986). Although the significance of the surface interaction is not known, several of these studies have proposed that it may have contributed to prolonged infection with *Salmonella* (LoVerde et al., 1980; Melhem and LoVerde, 1984). For a recent review discussing the mechanisms and pathological features of this interaction, see Muniz-Junqueira et al. (2009).

1.5. COINFECTION OF *SCHISTOSOMA* SPECIES WITH BACTERIA OTHER THAN *SALMONELLA*

Table 1.5 covers the interactions of *Schistosoma* spp. and bacteria other than *Salmonella* spp., including various *Mycobacterium* spp. (entry numbers 1–5), *Helicobacter pylori* (entry numbers 6–9), and *Staphylococcus aureus* (entry numbers 10–12). Most studies examined coinfection with *S. mansoni* (entry numbers 1, 4–7, 9–12); however, two studies examined coinfections with *S. haematobium* (entry numbers 3, 4) and one included *S. japonicum* bacteria interactions (entry number 8).

1.5.1. *Mycobacterium*

Three animal studies examined coinfection of *Schistosoma* and *Mycobacterium* species: two of these were experimental studies with mice (entry numbers 1, 5) and one studied a natural infection that occurred in sheep (entry number 2). Each study examined a different species of *Mycobacterium* as follows: *M. bovis*, *M. paratuberculosis* and *M. avium*. The two human studies examined coinfection with *Schistosoma* and *M. ulcerans* (entry numbers 3, 4).

1.5.1.1. Animal studies

The two animal studies (entry numbers 1, 2) examined interactions between *Schistosoma* and *M. bovis* or *M. paratuberculosis*. These studies found that coinfected hosts had more severe bacterial infections and showed greater mortality than singly infected hosts. The study on *M. bovis* (entry number 1) found that hosts coinfected with *S. mansoni* had an increased number of bacteria in the lungs, liver and spleen compared to animals with a single *M. bovis* infection; the authors hypothesized that prior infection with schistosomes may have impaired the Th1 immune response, thereby increasing susceptibility to the subsequent bacterial infection. The natural infection study in sheep showed greater mortality in the coinfected hosts, although pathological changes in the liver, small intestines and lungs and accompanying respiratory distress

TABLE 1.5 Coinfection studies of species of *Schistosoma* and bacteria other than *Salmonella*

Entry number	Reference	Species of trematode	Species of coinfecting organism	Experimental (E) or natural (N) infection in vertebrate hosts	Time between coinfections	Comments
Mycobacterium						
1	Elias et al. (2005)	*S. mansoni*	*Mycobacterium bovis*, BCG strain	(E) BALB/c mice	Sm followed by Mb (BCG strain) 8 wk later	Co mice had higher levels of bacteria in lungs, liver and spleen 6- to 15-wk post-challenge; Co mice had greater lung pathology compared to controls with single Mb infection; Sm increased susceptibility to Mb-BCG infection and impaired Th1 type response to mycobacterial antigen
2	Kataria et al. (2004)	*Schistosoma* sp.	*M. paratuberculosis*	(N) adult sheep	Unknown	Co hosts had 71% mortality; lung, liver and intestines infiltrated with schistosome eggs; lymphocytosis and leukocytosis in the sheep were indicative of chronic infection; severe respiratory distress attributed to underlying infection with schistosomiasis

3	Scott et al. (2004)	*S. haematobium*	*M. ulcerans*	(N) humans, ages not specified	Unknown	Patients with osteomyelitis were more likely to have Sh infection than patients without osteomyelitis; infection with Sh may have increased the severity of infection with Mu; no difference in detection rates between Mu in patients with and without Sh was noted
4	Stienstra et al. (2004)	*S. haematobium*, *S. mansoni*	*M. ulcerans*	(N) 2- to 53-year-old humans	Ma followed by Sm 60 days later	Patients with Mu had comparable levels of serum anodic antigens to schistosomes as controls without Mu; worm burdens from Sh or Sm were also comparable between those with and without Mu infection; Sh or Sm appeared not to increase susceptibility to Mu
5	Sacco et al. (2002)	*S. mansoni*	*M. avium*	(E) BALB/cAnN mice	Ma followed by Sm 60 days later	Co mice developed morphologically distinct hepatic granulomas; spleens of coinfected mice had granulomas with mycobacteria but not schistosome eggs; Co mice with prior Th1 response induced by Ma infection developed a Th2 response to infection by Sm but modulated subsequent coinfection with Sm

(*continued*)

TABLE 1.5 (*continued*)

Entry number	Reference	Species of trematode	Species of coinfecting organism	Experimental (E) or natural (N) infection in vertebrate hosts	Time between coinfections	Comments
Helicobacter pylori						
6	Elsaied et al. (2009)	*S. mansoni*	*Helicobacter pylori*	(E) albino mice	Sm followed by Hp 5 wk later	Co mice showed increased gastric pathological alterations compared to those with single Hp infection and higher mean total of worms than mice with single Sm infection; severity of Hp was exacerbated by coinfection with Sm
7	Abou Holw et al. (2008)	*S. mansoni*	*H. pylori*	(N) humans, age not specified	Unknown	Co patients had less severe gastritis and lower serum malondialdehyde (MDA) levels, a lipid peroxidation indicator, than patients with single Hp infection; higher MDA levels may be associated with carcinogenesis in gastric mucosa
8	Du et al. (2006)	*S. japonicum*	*H. pylori*	(N) 4- to 73-year-old humans	Unknown	Co subjects had a modified IgG serologic response to Hp compared to subjects with single Hp infection, with reductions noted in certain subclasses; modifications in Co subjects may have reduced the probability of developing gastric atrophy

9	Elshal et al (2004)	*S. mansoni*	*H. pylori*	(N) humans, ages not specified	Unknown	Co subjects had reduced DNA damage, reduced proliferation activity and reduced apoptosis compared with Hp patients alone indicating a reduction in gastric mucosal injury; infection with Sm may have modified an inflammatory response to Hp
Staphylococcus aureus						
10	Teixeira et al. (2001a)	*S. mansoni*	*Staphylococcus aureus*	(E) albino mice	Sm followed by Sa 60 and 120 days later	50% of mice coinfected during acute (60 days) phase and 47% of mice coinfected during chronic (120 days) phase of Sm infection developed liver abscesses; no abscess formation occurred in mice with either single infection or in uninfected controls during comparable time period; granuloma formation was seen in coinfected and single Sm infection groups
11	Mahmoud and Awad (2000)	*S. mansoni*	*S. aureus*	(E) Swiss albino mice	Sm followed by Sa at 9 or 16 wk	Co mice developed pyogenic liver abscesses compared with no development of abscesses in mice with either single infection; abscess formation highest in mice infected with Sa at 9wk after Sm infection (85%) versus mice infected with Sa at 16 wk (35%); abscess contained granulomas with Sm egg ova as well as Sa bacterial colonies

(*continued*)

TABLE 1.5 (*continued*)

Entry number	Reference	Species of trematode	Species of coinfecting organism	Experimental (E) or natural (N) infection in vertebrate hosts	Time between coinfections	Comments
12	Teixeira et al. (1996)	*S. mansoni*	*S. aureus*	(E) albino mice	Sm followed by Sa 60 days later	Seventy-seven percent of coinfected mice developed multiple hepatic abscesses; no abscesses present in single Sm or single Sa infections, or in uninfected controls; granuloma formation noted in Co mice and mice with single Sm infection; no pathological changes were noted in the livers of mice with single Sa infection or uninfected controls

Co, coinfected; Hp, *H. pylori*; Ma, *M. avian*; Mb, *M. bovis*; Mb-BCG, *M. bovis*-BCG; Mu, *M. ulcerans*; Sa, *S. aureus*; Sm, *S. mansoni*; Sh, *S. haematobium*; Sj, *S. japonicum*; unknown, not specified in original paper; wk, week or weeks.

were attributed to an infiltration by eggs of the *Schistosoma* species (entry number 2). The third study examined infection with *M. avium* followed by *S. mansoni* 60 days later; this study found that spleens of the coinfected mice with granulomas contained mycobacteria but not schistosome eggs. The authors hypothesized that based on the order of infection, the immune response in coinfected hosts was possibly modulated by the subsequent coinfection with *S. mansoni* (entry number 5).

1.5.1.2. Human studies

Two of three human studies that examined interactions between *S. haematobium* or *S. mansoni* and *M. ulcerans* also suggested that coinfection with *Schistosoma* spp. did not increase the susceptibility to the Mycobacterial infection (entry numbers 3, 4). The findings of one study, however, suggested that coinfection with *Schistosoma* spp. may have increased the severity of *M. ulcerans* since osteomyelitis occurred more frequently in the coinfected patients than those with only the bacterial infection (entry number 3). Osteomyelitis resulted from severe infection with *M. ulcerans* and often required the amputation of the affected limb. The other study examined the effect of *M. ulcerans* on a *Schistosoma* species infection and found comparable worm burdens in coinfected patients when compared to those with single *S. mansoni* or *S. haematobium* infections. For a further discussion of risk factors and immunological aspects of this coinfection, see the review of Stienstra et al. (2001), which also discussed the increasing problem of *Schistosoma* and Buruli ulcer infections in West African countries.

There have been several reports of hosts coinfected with schistosomiasis and gastrointestinal tuberculosis, including a recent account of a Laotian female immigrant in Australia presenting with clinical and histopathological characteristics similar to Crohn's disease (Kwan et al., 2009); an earlier report noted the difficulties in diagnosis of this coinfection in a patient from China (Labay et al., 1975). Cases of coinfection with schistosomiasis and pulmonary tuberculosis have also been noted (e.g. Olds et al., 1981; Sarwat et al., 1986; Gui et al., 1996, 1997). A number of studies have indicated that schistosomiasis in humans reduces the efficacy of the BCG vaccination; for recent reviews of helminths and mycobacteria, see Elias et al. (2007) and Sandor et al. (2003).

1.5.2. *Helicobacter pylori*

Three of four studies (entry numbers 7–9) were done on humans and indicated that an infection with *Schistosoma* species may have a protective effect on infection with *H. pylori*, since coinfected patients had less severe gastritis (entry number 7), reduced gastric mucosal injury (entry number 9) or modifications in serologic responses associated with lowered risk of developing gastric atrophy (entry number 8) than patients with single

H. pylori infection. The results were consistent with *H. pylori* coinfection studies and either *S. mansoni* (entry numbers 7, 9) or *S. Japonicum* (entry number 8). Two recent studies examined aspects of immune response between helminth infections and *H. pylori* in Colombian or African children; both found increased Th2 responses, which may be associated with decreased gastric cancer risk later in life (e.g. Cherian et al., 2010; Whary et al., 2005).

The findings of the experimental animal study (entry number 6) were in contrast to those on humans, with coinfected mice showing increased gastric pathological changes than mice with single *H. pylori* infection. The coinfected mice also had greater *S. mansoni* worm burdens than mice with single schistosome infections.

1.5.3. *Staphylococcus aureus*

These studies (entry numbers 10–12) were done on albino mice and examined infection with *Schistosoma* species followed by *S. aureus* at 60–63 or 112–120 days. In these studies, coinfected mice developed liver abscesses containing eggs of *Schistosoma* species and *S. aureus* bacteria, whereas no abscesses were found in singly infected hosts. Two studies (entry numbers 10, 12) compared abscess formation when *S. aureus* infection occurred during an acute (60–63 days) or chronic (112–120 days) *Schistosoma* species infection. One study (entry number 10) found no difference in the mean percent abscess formation between interval groups (50% vs. 47%), while the other (entry number 12) found a greater percentage of abscess formation when coinfection with *S. aureus* occurred with an acute *S. mansoni* infection (85%) rather than a chronic infection (35%).

Numerous reports (i.e. Goldani et al., 2005; Lambertucci et al., 1990, 1997; Sanchez-Olmedo et al., 2003; Teixeira et al., 1996, 2001b) have documented cases of pyogenic liver abscesses in children and adults coinfected with *Schistosoma* species and *S. aureus*; these reports are consistent with the results of the animal experiments reported above. For further discussion of these cases, see the review of Lambertucci et al. (1998, 2001).

1.6. COINFECTION OF *SCHISTOSOMA* AND *FASCIOLA* SPECIES

There are a total of 18 studies presented in Table 1.6, which examined coinfections with *S. mansoni*, *S. bovis* or *S. douthitti* and a *Fasciola* species, typically *F. hepatica* or *F. gigantica*. Fourteen of 18 studies were experiments done on a wide range of animals including mice, rats, cattle or calves, rabbits, lambs and goats (entry numbers 3, 5–9, 11–18); the remaining four studies were natural infections in human populations (entry numbers 1, 2, 4, 10).

TABLE 1.6 Coinfection studies on species of *Schistosoma* and *Fasciola*

Entry number	Reference	Species of trematode	Species of coinfecting organism	Experimental (E) or natural (N) infection in vertebrate hosts	Time between coinfections	Comments
1	Abou Holw et al. (2007)	*Schistosoma* sp.	*Fasciola* sp.	(N) humans, age not specified	Unknown	Co patients had serum gastrin levels that were 31–61% higher than patients with either single infection; alkaline phosphate activity was associated with higher egg counts from either parasite in all infected patients and with higher serum gastrin levels in the coinfected
2	Abou-Basha et al. (2000)	*S. mansoni*	*Fasciola* sp.	(N) humans, age not specified	Unknown	Co hosts had greater levels of precollege III peptide markers, an indicator of active or established fibrosis, than individuals with either single infection; children aged 5–14 years had more coinfections than adults as well as higher PIIIP levels; Co hosts had greater marked periportal fibrosis (23%) than those with single Sm (11%) or single *Fasciola* sp. (0%) combined

(*continued*)

TABLE 1.6 (*continued*)

Entry number	Reference	Species of trematode	Species of coinfecting organism	Experimental (E) or natural (N) infection in vertebrate hosts	Time between coinfections	Comments
3	Ferreras et al. (2000)[a]	*S. bovis*	*F. hepatica*	(E) Castellana lambs[b]	Sb followed by Fh 6 wk later (Sb/Fh); Fh followed by Sb 10 wk later (Fh/Sb)	Co Sb/Fh hosts had greater pathological changes in the liver and small intestines than hosts with Fh/Sb, or single Sb or Fh infections; Co Fh/Sb hosts had fewer Sb egg granulomas in the small intestine and fewer globular leukocytes but showed greater liver pathology than hosts with single Sb infection
4	Shousha et al. (1999)	*S. mansoni*	*Fasciola* sp.	(N) 12- to 30-year-old humans	Unknown	Co hosts had high levels of the free radicals super oxide and nitric oxide that were attributed to increased antigen stimulation with the dual infection; free radical production was lower in hosts with single *Fasciola* sp. infections than in hosts with single Sm infections
5	Rodriguez-Perez and Hillyer (1995)	*S. mansoni*	*F. hepatica*	(E) lambs	Sm followed by Fh 10 wk later	Co hosts had half the Fh worm burden than hosts with single Fh infections

6	Rodriguez-Osorio et al. (1993)[a]	*S. bovis*	*F. hepatica*	(E) Castellana lambs[b]	Sb followed by Fh 6 wk later (Sb/Fh); Fh followed by Sb 10 wk later (Fh/Sb)	Co Sb/Fh hosts had higher Fh worm burdens than hosts with single Fb infections and comparable Sh worm burdens to single Sb-infected hosts; conversely, Co Fh/Sb hosts had a lower Sb worm burden than hosts with single Sb infections
7	Haroun and Hillyer (1988)	*S. mansoni*	*F. hepatica*	(E) lambs	Sm followed by Fh 10 wk later	Co hosts had a 51% reduction in Fh worm burden than hosts with single Fh infections; Co hosts also had higher total leukocyte and eosinophil counts, than controls, but showed less hepatic damage
8	Ford et al. (1987)	*S. mansoni* (irradiated and non-irradiated)	*F. hepatica*	(E) PVG rats and Fischer F344 rats, New Zealand white rabbits[b]	Sm followed by Fh 29 days later; Fh followed by Sm 28 days later	Co rats with prior Sm infection had 28–33% reduction in Fh than rats with single Fh infection; Co rats (both strains) with prior Fh infection had 66–69% reduction in Sm burden than rats with single Sm infection; exposure to metacercariae or juvenile worms stimulated resistance, while irradiated Sm cercariae and adults worms did not
9	El Sanhouri et al. (1987)	*S. bovis* (irradiated)	*F. gigantica*	(E) Nubian goats[b]	Sb followed by Fg 8 wk later	Co hosts with prior Sb infection from irradiated cercariae had comparable Fg worm burden to hosts with single Fg infection; prior infection with irradiated cercariae from Sb did not reduce the subsequent worm burden from Fg

(*continued*)

TABLE 1.6 (*continued*)

Entry number	Reference	Species of trematode	Species of coinfecting organism	Experimental (E) or natural (N) infection in vertebrate hosts	Time between coinfections	Comments
10	Salem et al. (1987)	*S. mansoni*	*Fasciola* sp.	(N) humans, age not specified	Unknown	Co patients with fascioliasis had higher IgM and lower IgG levels than patients with single Fasciola sp. infections; IgE levels were comparable in both single and double infection groups; immunoglobin levels were not correlated with egg counts
11	Yagi et al. (1986)	*S. bovis* (irradiated and non-irradiated)	*F. gigantica*	(E) Zebu cattle[b]	Sb followed by Fg 8 wk later; Fg followed by Sb 8 wk later	Co cattle with Sb had 83% reduction in Fg compared to hosts with single Fg infection; non-irradiated Sb cercariae produced resistance, but irradiated Sb cercariae did not; Co cattle with Fg had 92% reduction in Sb compared to hosts with single Sb infection
12	El-Azazy and Van Veen (1985)	*S. mansoni*	*F. hepatica*	(E) rats, strain not specified	Sm followed by Fh 8 wk later	Co rats with prior Sm infection had fewer Fh worms and less pathological changes associated with Fh than rats with single Fh infection
13	Hillyer (1981)	*S. mansoni*	*F. hepatica*	(E) GP albino mice[b]	Sm followed by Fh at 3, 5 or 7 wk	Mice coinfected with Sm at 5 or 7 wk had 62% or 71–89% reduction in Fh worm burden compared to mice

						with single Fh infection; no difference between single and double infection groups noted at 3-wk interval; Fh had no effect on existing Sm infection
14	Monrad et al. (1981)	*S. bovis*	*F. hepatica*	(E) lambs	Sh followed by Fh at 2–3, 7–8 or 16–17 wk later	Sheep coinfected with Fh at 2–3 or 7–8 wk had 93% and 70% fewer Fh worms than sheep with single Fh infection; sheep coinfected with Fh at 16–17 wk had comparable Fh worm burden to the controls; Co hosts had reduced Fh-induced liver damage compared to the controls; Sm egg burden was comparable between single and double infections
15	Sirag et al. (1981)	*S. bovis*	*F. hepatica*	(E) Jersey calves[b]	Sb followed by Fh 10 wk later	Co calves had 30% reduction in worm burden and less sever hepatobiliary damage compared with calves with single Fh infection
16	Christensen et al. (1980)	*S. mansoni*	*F. hepatica*	(E) SVS albino mice[b]	Sm (single sex) followed by Fh 22–76 days later; Sm (mixed sex) followed by Fh 46 days later; Sm (mixed sex)	Co hosts with a single sex Sm (male or female) infection had comparable Fh worm burdens to hosts with single Fh infection; Co hosts with mixed sex Sm infection had 61% reduction in Fh worms compared to controls; hosts infected simultaneously or up to 48 h apart had a reduction in Sm worms

(*continued*)

TABLE 1.6 (*continued*)

Entry number	Reference	Species of trematode	Species of coinfecting organism	Experimental (E) or natural (N) infection in vertebrate hosts	Time between coinfections	Comments
					followed by Fh concurrently or 48 h later	(40–43%) but not in Fh burden compared to the controls
17	Christensen et al. (1978)	*S. mansoni*	*F. hepatica*	(E) SVS albino mice[b]	Sm followed by Fh 7–28 or 54–65 days later; Fh followed by Sm 7–23, or 28–50 days later	Hosts with pre-patent Sm infections had comparable Fh worm burden to controls, while hosts with patent Sm infection had 34–76% reductions in Fh worms; similarly, hosts with pre-patent Fh infection had comparable Sm worm burdens to controls; hosts with patent Fh infection had 41–50% reductions in Sm worms
18	Maldonado-Moll (1977)	*S. douthitti*	*F. hepatica*	(E) albino mice	Sd followed by Fh 25 days later; Fh followed by Sd 20 days later	Livers of Co mice observed 55 days after initial Sd infection (followed by Fh) had decreased Fh unembryonated eggs and increased dead eggs compared to controls; similarly, livers of Co mice observed 45 days after initial Fh infection (followed by Sd) had a greater number of dead Sd eggs compared to controls

Co, coinfected; Fg, *F. gigantica*; Fh, *F. hepatica*; Sb, *S. bovis*; Sd, *S. douthitti*; Sj, *S. japonicum*; Sm, *S. mansoni*; unknown, not specified in original paper; wk, week or weeks.
[a] These two studies use the same study group and are discussed as one in our text.
[b] See original papers for more information on the breeds and strains of hosts used.

1.6.1. Animal studies

An infection with a *Schistosoma* species followed by an infection with *Fasciola* was examined in all 14 studies, with the interval between coinfection ranging from 2 to 17 weeks later depending in part on the species of host animal used in the study. Most of the rodent studies used *S. mansoni* for the *Schistosoma* species (entry numbers 8, 12, 13, 16, 17), with one study using the murine schistosome *S. douthitti* (entry number 18). These studies were consistent in findings that mice or rats with a 5- to 8-week *Schistosoma* infection had reduced (up to 89%) *Fasciola* worm burdens than singly infected hosts (entry numbers 12, 13, 16, 17). One study reported that rats with a 4-week *Schistosoma* infection had some reduction in *Fasciola* worm burden (up to 33% reported, entry number 8); no differences in worm burdens were reported at 1–4 weeks in mice (entry numbers 13, 17). Mice that were concurrently infected or infected with *Fasciola* up to 48 h after being infected with *Schistosoma* had 40–43% reductions in *Schistosoma* worm burden, indicating that the interval between coinfection may not have a simple linear association (entry number 16). The apparent protective effect may only be found in mixed sex schistosome infections, since single sex *Schistosoma* failed to induce any reductions in *Fasciola* worm burdens during the expected time period (entry number 16).

The two studies done on lambs also found reductions (up to 51%) in *Fasciola* worm burdens when an infection with *Fasciola* followed a patent *S. mansoni* infection (entry numbers 5, 7). The other two lamb studies, however, examined an infection *S. bovis* followed by an infection with *F. hepatica* 2–17 weeks later with conflicting results (entry numbers 3, 6, 14). Contrary to the findings of the rodent studies, one study (entry number 14) found that hosts with pre-patent *Schistosoma* infections had greater reductions in *Fasciola* burden (up to 93%) than hosts with a patent infection (70%), with no reductions observed at all in hosts with chronic (16–17 week) *Schistosoma* infections. Based on these findings, the authors hypothesized that pre-patent schistosomes were responsible for the resistance to *Fasciola* rather than the adult schistosome worm (entry number 14). Contrary to all other reported animal studies, one study found increased *Fasciola* burdens when coinfection followed a 6-week *Schistosoma* infection in lambs (entry numbers 3, 6). Two large animal studies examined an *S. bovis* infection followed by Fasciola were largely consistent with most rodent reports, indicating reductions in *Fasciola* worm burden in cattle (83% for an 8-week interval, entry number 11) and calves (30% reduction for a 10-week interval, entry number 15). Reductions of worm burden in pre-patent infections were not examined in these studies.

The above studies indicate that the timing interval between coinfections is important as well the species of *Schistosoma* and/or the host. In studies using *S. mansoni*, the highest reductions in *Fasciola* occurred

when it followed a patent infection with *S. mansoni*; these studies mainly involved mice, rats and lambs. Whereas in studies involving *S. bovis*, the greatest reductions occurred in pre-patent infections; these studies involved calves, cattle and lambs. Some of these studies reported that the reductions in *Fasciola* burden were accompanied by fewer pathological changes in the coinfected host (entry numbers 12, 14, 15, 18), including a decrease in *F. hepatica* unembryonated eggs in the liver (entry number 18) and less severe *Fasciola*-induced liver hepatobiliary damage (entry numbers 14, 15). The one study that reported an increase in worm burden also noted greater pathological changes in the liver and small intestines in coinfected hosts (entry numbers 3, 6). Several studies discussed above reported that prior infection with irradiated *Schistosoma* cercariae failed to produce a reduction in *Fasciola* burden (entry numbers 8, 9, 11).

The seven experimental studies that examined hosts *Fasciola* infections followed by an infection with *Schistosoma* found reduced worm burdens (up to 92%) for the subsequent infection (entry numbers 3, 6, 8, 11, 17, 18), particularly when following a patent *Fasciola* infection (entry numbers 3, 6, 11, 17). Two studies also reported fewer *S. mansoni* eggs in the small intestines of lambs (entry numbers 3, 6) and a greater number of dead *S. douthitti* eggs in the liver of the mouse (entry number 18). Reductions in *S. bovis* worm and egg burden in the lambs were also accompanied by greater liver pathology in these coinfected hosts, indicating that reductions in worm and egg burden may not be associated with fewer pathological changes in the coinfected host (entry numbers 3, 6).

1.6.2. Human studies

The four studies examining natural infections on human populations (entry numbers 1, 2, 4, 10) each studied different aspects of the effect of coinfection, but findings generally indicated increased immunological and pathological responses in the coinfected host. One study found that coinfected hosts had greater periportal fibrosis as well as higher associated levels of procollagen III peptide markers than single hosts, with the highest levels occurring in children 5–14 years of age (entry number 2). Similarly, other studies found that coinfected patients had higher egg counts which was accompanied by higher serum gastrin levels (entry number 1) and higher levels of free radicals associated with the inflammatory response (entry number 4). Coinfected hosts with fascioliasis had higher IgM and lower IgG levels than patients with single *Fasciola* levels, and these levels were not correlated with *Fasciola* egg counts (entry number 10).

The few prevalence reports (e.g. Curtale et al., 2007; Esteban et al., 2003) of coinfection with *Schistosoma* and *Fasciola* in hyperendemic areas such as Egypt indicate that such coinfections may be rare in human populations; reports in the veterinary literature indicate that such

coinfections may be common in cattle in some parts of the world, for example, Zambia (Yabe et al., 2008) and that the clinical presentation in other large game such as the Zebu in Senegal includes anaemia and weight loss (Kaboret et al., 1993).

1.7. COINFECTION OF *SCHISTOSOMA* SPECIES AND HELMINTHS OTHER THAN THE GENUS *FASCIOLA*

Table 1.7 presents coinfection studies on *Schistosoma* and various helminths other than *Fasciola*, including echinostomatids in the genus *Echinosoma* (entry numbers 1–5) and various nematodes including hookworm species, that is (entry numbers 6–11) *Necator americanus* and *Ancylostoma* spp., *Trichuris* (entry numbers 12–15), *Ascaris* spp. (entry numbers 16–18), *Strongyloides* and *Trichostrongyloides* (entry numbers 19–22) and filarids (entry numbers 23–25) including *Brugia pahangi*.

1.7.1. *Echinostoma*

All five coinfection studies on *Schistosoma* and *Echinostoma* were done in Balb/C or other strains of albino mice; one study used the water rat, *Nectomys squamipes* (entry number 1). These studies examined the effect of coinfection on both *S. mansoni* (entry numbers 1–5) or *S. bovis* (entry number 5) and *E. caproni* (entry numbers 2–5) or *E. paraensei* (entry number 1).

Two of five studies examined the effect when *Schistosoma* was followed by an infection with *Echinostoma* at intervals of 1–14 weeks. Mice with a patent or chronic *Schistosoma* infection had a 73% or a 100% reduction (respectively) in the *Echinostoma* infection compared to controls (entry number 5), while mice with a pre-patent *Schistosoma* infection had no comparable reduction in infection (entry numbers 3, 5). Two studies (entry numbers 1, 5) examined the effect when *Echinostoma* was followed by an infection with *Schistosoma* at 2- to 6-week intervals. Here, mice with a 6-week-old *Echinostoma* infection had a reduced *Schistosoma* infection compared to the controls (entry number 1), while mice and rats with a 2- or 3-week infection showed no comparable reduction in *Schistosoma* (entry number 5). Increased *Schistosoma* worm burdens were noted when the schistosome infection followed that of *Echinostoma* at 2 weeks (entry number 1) or 33 days (entry number 4). These results suggest that only patent schistosome infections confer protection against *Echinostoma* or could be attributed in part to differences in the strain of *Schistosoma* used in the experiments. In regard to possible strain differences, one of the studies found that rats had a heavier early worm burden when the wild RJ strain of *Schistosoma* was used rather than the BH lab strain (entry number 1). Finally, one study examined the effect on pregnant mice concurrently infected with *S. mansoni*

TABLE 1.7 Coinfection studies on species of *Schistosoma* and helminths other than *Fasciola*

Entry number	Reference	Species of trematode	Species of coinfecting organism	Experimental (E) or natural (N) infection in vertebrate hosts	Time between coinfections	Comments
Echinostoma						
1	Maldonado et al. (2001)	*S. mansoni* (wild RJ and BH lab strain)[a]	*Echinostoma paraensei*	(E) *Nectomys squamipes* (water rat)[a]; Swiss-Webster albino mice	Rat: Ep followed by Sm at 4 wk; mouse: Ep followed by Sm at 2 or 6 wk	Rats showed different susceptibility depending on Sm strain; Co rats with RJ strain of Sm had greater Sm worm burdens than controls, but parasitism was not affected with Bh strain; reduction in Sm (either strain) was noted in coinfected mice when followed by Sm at 6 wk; Ep infection appeared to interfere with development of Sm in a strain-dependent manner in some rodents; earlier increase in Sm was noted when mice were coinfected at 2 wk
2	Bindseil et al. (1989)[b]	*S. mansoni*	*Echinostoma caproni*	(E) BALB/cABom mice	Concurrently coinfected	Co pregnant mice had a lower number of live foetuses than pregnant mice without coinfection; mean foetal weight was lower in coinfected hosts than in controls

3	Christensen et al. (1985)[b]	*S. mansoni*	*E. caproni*	(E) albino SS and SVS mice	Sm followed by Ec 4 wk later	Expulsion of low-level Ec was impaired in mice harbouring pre-patent Sm infection compared to mice with single Ec infection; timing of expulsion was dependent on strain and age of mice
4	Christensen et al. (1981)[b]	*S. mansoni*	*E. caproni*	(E) SVS albino mice	Ec followed by Sm 20–33 days later	Co mice had increased Sm worm burdens compared to mice with a single Sm infection; the increase in Sm worm burden was greatest in mice with 33-day-old Ec infections (91%) compared to controls
5	Sirag et al. (1980)[b]	*S. mansoni*, *S. bovis*	*E. caproni*	(E) SVS albino mice	Sm or Sb followed by Ec 7–99 days later; Ec followed by Sm 14 or 21 days later	Mice infected with Sm followed by Ec 43 days later had a 73% reduction in Ec infection compared to mice with a single Ec infection; mice coinfected with Ec at 79 or 99 days after Sm had 100% reduction in Ec compared to controls; Sb infection or pre-patent Sm infection had no effect on subsequent Ec infection; prior infection with Ec had no effect on subsequent infection with Sm

(*continued*)

TABLE 1.7 (*continued*)

Entry number	Reference	Species of trematode	Species of coinfecting organism	Experimental (E) or natural (N) infection in vertebrate hosts	Time between coinfections	Comments
Hookworm						
6	Wu et al. (2010)	*S. japonicum*	*Necator americanus*	(E) golden hamster	Concurrently coinfected	Co hosts had comparable worm burdens to hamsters with single infection but showed altered metabolic profiles including depleted amino acids and glucose in sera, and gut-related metabolites; changes may induce pathological changes (e.g. liver damage, anaemia) in Co hosts
7	Pullan et al. (2010)	*S. mansoni*	*N. americanus*	(N) children and adult humans, ages not specified	Unknown	There was no evidence that host genetics modulated the intensity of coinfection in endemic areas; a high positive correlation between Sm and Na egg counts was noted in coinfected hosts; a strong correlation between intensity of infections in Co hosts was noted

8	Ezeamama et al. (2008)	*S. japonicum*	Hookworm (species not designated)	(N) 7- to 18-year-old humans	Unknown	Co hosts had higher levels of anaemia than subjects with either single infection; coinfection results were suggestive of multiplicative effects on anaemia in hosts
9	Fleming et al. (2006)	*S. mansoni*	*N. americanus*	(N) mostly <40 years humans	Unknown	Subjects with heavy hookworm infections also showed heavy coinfections with Sm; Co subjects had higher Sm egg burdens than subjects with single Sm infection; infections appeared heaviest in individuals aged 10 years and older
10	Keiser et al. (2002)	*S. mansoni*	Hookworm (species not designated)	(N) human children	Unknown	High positive correlation between intensity of infection with Sm and coinfection with hookworm in study subjects, especially among older children; repeated faecal egg counts were necessary to determine the extent of coinfection

(*continued*)

TABLE 1.7 (*continued*)

Entry number	Reference	Species of trematode	Species of coinfecting organism	Experimental (E) or natural (N) infection in vertebrate hosts	Time between coinfections	Comments
11	Chamone et al. (1986)	*S. mansoni*	*Ancylostoma* sp.	(N) 18- to 50-year-old humans	Unknown	More than half of the patients with chronic Sm infection were also coinfected with *Ancylostoma*; Co hosts had higher mean Sm egg output than patients with single Sm infections
Trichuris						
12	Bickle et al. (2008)	*S. mansoni*	*Trichuris muris*	(E) AKR mice	Tm followed by Sm 40 days later	Co hosts had altered cytokine response to Sm in their lungs and livers; greater number of Sm worms and eggs found in the liver of Co hosts; results of the study suggest that pre-existing Tm infection facilitated survival and increased migration of Sm to the hepatic portal system
13	Ezeamama et al. (2008)	*S. japonicum*	*T. trichiura*	(N) 7- to 18-year-old humans	Unknown	Co hosts showed higher levels of anaemia than subjects with either single infection; coinfection induced additive effects on anaemia in hosts

14	Curry et al. (1995)	*S. mansoni*	*T. muris*	(E) AKR mice[a]	Sm followed by Tm 56 days later; Tm followed by Sm 3, 7, 21 and 31 days later	Mice with an established Sm infection had lower Tm worm burdens and an increased ability to resolve a subsequent infection by Tm compared to mice with single Tm infection; this response was linked to a stronger Th2 and lower Th1 response in Co hosts; alterations in Th1 profile were also found in mice infected with Tm followed by Sm
15	Parraga et al. (1996)	*S. mansoni*	*Trichuris* sp.	(N) 7- to 15-year-old humans	Unknown	Subjects with Sm were more likely to be coinfected with *Trichuris* than subjects without Sm infection; Co subjects were more prone to malnutrition than subjects without coinfection
Ascaris sp.						
16	Fleming et al. (2006)	*S. mansoni*	*Ascaris lumbricoides*	(N) less than 1- to over 40-year-old humans	Unknown	Fewer subjects were coinfected with Sm and Al, than were infected by Sm or Al as single infections; Co hosts had lower Sm egg burdens than single infected subjects with Sm; no difference in rate of infection was noted between age groups

(*continued*)

TABLE 1.7 (*continued*)

Entry number	Reference	Species of trematode	Species of coinfecting organism	Experimental (E) or natural (N) infection in vertebrate hosts	Time between coinfections	Comments
17	Parraga et al. (1996)	*S. mansoni*	*Ascaris* sp.	(N) 7- to 15-year-old humans	Unknown	No significant effects of the coinfection on the nutritional status of the hosts were noted; Co boys and girls had *Ascaris* burdens that were comparable to children without *Schistosoma* infections
18	Helwigh and Bogh (1998)	*S. japonicum*	*A. suum*	(E) Danish cross-bred pigs[a]	Sj followed by As 11 or 16 wk later	Co pigs had fewer As induced white spots on the liver than pigs with single As infection; Sj may have suppressed gross pathological changes from As or inhibited host immune response to As; Co pigs had comparable levels of As larvae in lungs, liver and small intestines as the controls

Strongyloid/Trichostrongyloid nematodes						
19	Bazzone et al. (2008)	*S. mansoni*	*Heligmosomoides polygyrus*	(E) CBA and BL/6 mice	Hp at 4 wk and at 2 days prior to Sm infection	Co CBA mice had smaller hepatic granulomas and a reduced immune response to Sm infection but showed comparable Sm worm and egg burdens compared to mice with a single Sm infection; prior infection with Hp reduced the severity of the Sm infection
20	Gazzinelli and Melo (2008)	*S. mansoni*	*Strongyloides venezuelensis*	(E) AKR/J mice	Sm followed by Sv 45 days later	Co mice had fewer Sv larvae in their lungs and fewer female worms in their intestines compared to mice with single Sv infection; female Sv worms in Co hosts were smaller and less fertile than Sv worms recovered from mice with single Sv infection; prior infection with Sm decreased subsequent infection by Sv
21	Maruyama et al. (2000)	*S. japonicum*	*S. venezuelensis*	(E) C57BL/6 mice	Sj followed by Sv 6 wk later; other times tested but not specified	Mice infected with Sj showed strong protective immune response to subsequent infection with Sv; Co mice eliminated intestinal Sv infection faster than mice with single Sv

(*continued*)

TABLE 1.7 (*continued*)

Entry number	Reference	Species of trematode	Species of coinfecting organism	Experimental (E) or natural (N) infection in vertebrate hosts	Time between coinfections	Comments
22	Yoshida et al. (1999)	*S. mansoni*	*S. venezuelensis*	(E) BALB/c and C57BL/6 mice	Sm followed by Sv 3, 6, 9 or 12 wk later	Co mice had fewer Sv larvae in their lungs and far fewer adult worms in the small intestines compared to mice with single Sv infection; no worms were recovered in Co mice 9 wk after Sm infection; immune response from prior infection with Sm appeared to protect from subsequent infection with Sv
Filarid nematodes						
23	Sato et al. (1989)	*S. mansoni*	*Brugia pahangi*	(E) Mongolian jird[a]	Bp followed by Sm 17 days or 39 wk later	Co girds with acute (17 days) Bp infection showed comparable Sm worm recovery to girds with single Sm infection; some Co girds with chronic (39 days) Bp had increased number of Sm eggs in the stool but comparable level of worms than girds with single Sm infection; infection with Bp appeared not to enhance the susceptibility of hosts to subsequent infection with Sm

24	el-Hawey et al. (1986)	*Schistosoma* sp.	Unidentified filarid species	(N) humans, age not specified	Unknown	Co subjects had higher fever, abdominal distention, joint pains, dysentery and anaemia than subjects with either single infection; Co hosts were more likely to have elephantiasis than subjects with single filiarial infections; Co had lower egg counts and was less likely to have liver or spleen involvement than subjects with single *Schistosoma* infections
25	Mohamed et al. (1983a), Mohamed et al. (1983b)	*S. haematobium*, *S. mansoni*	Unidentified larval and adult filarid species	(N) humans, age not specified	Unknown	Co subjects with microfilariae had higher serum C3 levels than subjects with either single infection; Co subjects with adult filarids had higher serum C4 levels than subjects with either single infection; Co subjects were more likely to have elephantiasis than singly infected subjects, with highest prevalence among females and subjects under 30 years of age

Co, coinfected; Al, *A. lumbricoides*; As, *A. suum*; Bp, *B. pahangi*; Ec, *E. caproni*; Ep, *E. paraensei*; Hp, *H. polygyrus*; Na, *N. americanus*; Sb, *S. bovis*; Sh, *S. haematobium*; Sj, *S. japonicum*; Sm, *S. mansoni*; Sv, *S. venezuelensis*; Tm, *T. muris*; Tt, *T. trichuris*; unknown, not specified in original paper; wk, weeks.

[a] See original papers for more information about the breeds and strains of hosts used.

[b] *Echinostoma caproni* is referred to in this study as *Echinostoma revolutum*.

and *E. caproni* and found that coinfected mice had a lower number of live foetuses than pregnant mice without the coinfection; the mean foetal weight was also lower in the coinfected hosts (entry number 2).

In summary, a patent infection with either *Schistosoma* or *Echinostoma* appeared to reduce the burden of the subsequent infection by the other trematode, whereas there was no effect or possibly an increased burden of the subsequent infection when worms were introduced during the prepatent phase of the first infection. In several studies, the authors noted that the age and strain of the rodent host used was an important factor in these coinfection studies (entry numbers 1, 3).

1.7.2. Hookworm

Five of six studies were natural infections in children and adults: four examined hookworm coinfection with *S. mansoni* (entry numbers 7, 9–11) and one studied hookworm and *S. japonicum* (entry number 8). These studies included various hookworm species, identified in three studies as *N. americanus* (entry numbers 7, 9) and as a *Ancylostoma* sp. in one study (entry number 11). One study (entry number 6) examined an experimental coinfection between *S. japonicum* and *N. americanus* in the Golden Hamster. The studies on humans consistently found a strong association between the schistosome and the hookworm infections, with greater *Schistosoma* egg counts and worm burdens reported mainly in hosts with the heaviest hookworm infections (entry numbers 7, 9–11). In two studies, children aged 10 or older had some of the heaviest coinfection burdens (entry numbers 9, 10). Coinfected children also had an increased anaemia compared to singly infected children; the possibility of a multiplicative schistosome–hookworm interaction, that is, the combined effect of the coinfection being greater than the sum of either infection was suggested by several studies (entry numbers 8, 9, 11). The sole experimental schistosome–hookworm study (entry number 6) found that coinfected hamsters had comparable worm burdens to singly infected control hosts; the coinfected hosts also had altered metabolic profiles that may have been associated with pathological changes in the liver or anaemia. The interval between coinfection was unknown in the human studies, while the hamsters were infected concurrently in the experimental schistosome–hookworm study.

1.7.3. *Trichuris*

1.7.3.1. Animal studies

Coinfection interactions with *Schistosoma* were examined in two experimental mouse studies using *T. muris* (entry numbers 12, 16) and two natural infection studies in humans with *T. trichiura* (entry numbers 13, 15).

Both murine studies examined the immune response and the effect when *T. muris* was followed by *S. mansoni* (entry number 12, 14); one study also focused on *S. mansoni* followed by *T. muris* (entry number 14). The two human studies examined the effects of coinfection in which the interval between the first and the second infection was not given; one study examined *T. trichiura* with *S. mansoni* (entry number 15) and the other *T. trichiura* with *S. japonicum* (entry number 13).

In entry number 12, mice with a chronic (40 days) *T. muris* infection had an increased burden of *Schistosoma* worms and eggs in their livers compared to singly infected mice. An immune response to *T. muris* dominated the coinfected animals and an altered response to *S. mansoni* was found in both the lungs and the livers. The prior infection with *T. muris* appeared to enhance the migration of both male and female schistosomes to the hepatic portal system, thus increasing the severity of the *Schistosoma* infection. The other study (entry number 14) found that coinfection altered the parasite-specific immune response, with the greatest effect noted on the second infection. In this study, mice infected with *S. mansoni* followed by infection with *T. muris* 56 days later showed an established Th2 response that increased the ability of these mice to resolve the secondary infection. In this study, coinfected hosts had lower *T. muris* worm burdens than singly infected *T. muris* controls which had a dominant Th1 response.

1.7.3.2. Human studies

The two natural infection studies on children found that coinfected hosts had more severe anaemia (entry number 13) and malnutrition (entry number 15) than singly infected subjects. The severity of the anaemia appeared additive in nature, that is, equal to that of singly infected children with either infection added together (entry number 13). In entry number 15, children with *S. mansoni* were more likely to have *T. trichuris* coinfection than subjects without the *Schistosoma* infection, suggesting that susceptibility to trichuris infection may be increased by coinfection.

1.7.4. *Ascaris*

The three studies in this table examined the coinfections between *Schistosoma* species and *Ascaris* species: two were natural infection studies in humans (entry numbers 16, 17) and one was an experimental study in pigs (entry number 18). The two human studies examined different aspects of coinfection between *S. mansoni* and *Ascaris* species, identified in one of study as *A. lumbricoides*. One study (entry number 16) reported that coinfected hosts had lower *S. mansoni* egg burdens than subjects with single *Schistosoma* infections; it also reported that coinfection with

Schistosoma and *Ascaris* occurred less often than single infections with either species in this population. The other study (entry number 17) focused on the *Ascaris* worm burden, finding comparable burdens of *Ascaris* infection in those with and without *Schistosoma*. Both papers noted that there was no difference in the percent infected between age groups (entry number 16) or between males and females (entry number 17). Both the order and the interval between infections were unknown in either study. The experimental study examined the effect of an infection with *S. japonicum* followed by an infection with *A. suum* 11 or 16 weeks later in Danish cross-bred pigs (entry number 18). In this study, the coinfected pigs had fewer *A. suum*-induced white spots on the liver but comparable levels of *Ascaris* larvae in the lungs, liver and small intestines as controls. The authors concluded that it was possible that a prior infection with *S. japonicum* may have suppressed gross pathological changes associated with *Ascaris* or in some way inhibited the host immune response.

A number of prevalence studies have examined the worm burden of coinfection with schistosomes and *Ascaris*, *Trichiura* or hookworm and reported results that are largely consistent with those discussed above. Coinfection with hookworm and *Schistosoma* in children is common in many locations including Brazil, China, Kenya and Tanzania, while coinfection with *Schistosoma* and *Trichiura* or *Schistosoma* and *Ascaris* occurs less often in endemic areas (e.g. Brito et al., 2006; Brooker and Clements, 2009; Brooker et al., 2000; Chamone et al., 1990; Ellis et al., 2007; Hamm et al., 2009; Lwambo et al., 1999; Nguhiu et al., 2009). For a recent review discussing these studies and additional immunological factors, see Geiger (2008).

1.7.5. *Strongyloides* and *Trichostrongyloides*

The four experimental studies (entry numbers 19–22) involving strongyloid and trichostrongyloid nematodes examined coinfection with *S. mansoni* or *S. japonicum* and either *Strongyloides venezuelensis* or *Heligmosomoides polygyrus* in various strains of mice. Three of four studies (entry numbers 20–22) examined a *Schistosoma* infection followed by an infection with *S. venezuelensis* 3–12 weeks later; these studies found that the first infection decreased the severity of the subsequent *Strongyloides* infection. These studies also found that coinfected hosts had decreased numbers of strongyloid larvae in their lungs and a decreased adult worm burden in the small intestines (entry numbers 20–22), with smaller and less fertile *S. venezuelensis* females (entry number 20). The greatest reduction in worm burden in the *Strongyloides* infection occurred when infection followed a 6- to 9-week *Schistosoma* infection (entry numbers 21, 22). A similar effect was observed for both *S. mansoni* and *S. japonicum* and did not seem to vary with

mouse strain. One study examined a prior infection with *H. polygyrus* followed by infection with *S. mansoni* 2 days and 4 weeks later; in this study, infection with *H. polygyrus* reduced the severity of the subsequent *Schistosoma* infection, with a reduced schistosome worm burden and smaller hepatic lesions in the coinfected animals compared with the controls (entry number 19).

In this interaction, infection with one helminth in an experimental setting seemed to confer protection from a subsequent infection with the other helminth; as observed in other helminth interactions, worm age associated with the first infection is important, with patent infections tending to confer the greatest protection. Natural coinfections in human populations do occur. A recent prevalence survey found that over 9% of Sudanese refugees were coinfected with *Schistosoma* and *Strongyloides* (Brodine et al., 2009), and several case reports illustrate a variety of clinical presentations from coinfection (e.g. Fairweather et al., 2010; Olson and Domachowske, 2006; Tzanetou et al., 2005).

1.7.6. Filarids

The past three studies in this table examined coinfections of *Schistosoma* species and filarids: one was an experiment done on girds with *B. pahangi* (entry number 23); the other two studies were natural infections in humans with unidentified filarids (entry numbers 24, 25). Two studies identified the schistosomes as *S. mansoni* (entry numbers 23, 25) or *S. haematobium* (entry number 25); the other did not identify the schistosome species (entry number 24). The findings of the two human studies were consistent, indicating that coinfected subjects had altered immune responses and pathological changes compared to subjects with single filarid infections. Coinfected subjects were more likely to have elephantiasis (entry numbers 24, 25) and increased fever, anaemia, joint pains and other clinical symptoms associated with filariasis (entry number 24) than subjects with a single filarid infection; one of the studies (entry number 24) also examined the effect of the coinfection on the *Schistosoma* infection and found that the coinfected were less likely to have liver and spleen involvement from than singly infected *Schistosoma* controls. While coinfection appeared to increase the severity of filariasis, it may be associated with a reduction in the severity of the *Schistosoma* infection.

The experimental study (entry number 23) examined the effect of a prior infection of *B. pahangi* followed by subsequent infection with *S. mansoni* 17 or 39 days later; it did not find much difference in the comparison groups other than a modest increase in the number of *S. mansoni* eggs in the stool of coinfected girds with chronic *B. pahangi* infection. The coinfected girds had a comparable number of *S. mansoni* worms as the controls, regardless of the time interval between coinfection.

1.8. CONCLUDING REMARKS

Numerous factors influence the effects of coinfection on the vertebrate host with *Schistosoma* and protozoa, bacteria or other helminths. Some of these factors are as follows: organisms and hosts used in the studies, order and time interval between the first and the second infection, studies on natural versus experimental hosts, dosage of the infectious agents, strains and pedigrees of the parasites, age of hosts at time of exposure to the infectious agents and age of hosts at the time of necropsy.

Broad generalizations on the effects of coinfection on vertebrate hosts are difficult to make. However, some trends based on our review for the most studied aspects of coinfection are worth noting. A prior infection with *Schistosoma*, particularly a patent infection, often has an effect on the subsequent infection by a protozoan, bacterium or other helminth. In relatively few cases, a prior infection with *Schistosoma* decreased the severity of the subsequent infection as with *H. pylori*, *F. hepatica*, *Echinostoma* or *Plasmodium*, the latter only exhibiting this behaviour when coinfected with *S. haematobium*. More often, however, a prior infection with *Schistosoma* increased the severity of the second infection as with *Leishmania*, *T. gondii*, *E. histolytica*, *S. aureus* or *Salmonella*. The severity of a *Plasmodium* infection was also increased when it followed a prior infection with *S. mansoni*. In some of these coinfection studies, the increased severity of the subsequent infection was associated with a specific, prolonged form of the disease in humans, for example, osteomyelitis associated with *M. ulcerans*, elephantiasis associated with certain filarids, non-typhoidal salmonellosis appearing with typhoidal severity associated with *Salmonella* and pyogenic liver abscesses associated with *S. aureus*. The severity of this effect may be due to the subsequent coinfecting organism being contained within the *Schistosoma* worms or associated with schistosome-induced granuloma, as in the case of coinfection with *Salmonella*, *S. aureus* or *Leishmania*. It may also be due to the subsequent coinfecting organism taking advantage of prior physical damage caused by the *Schistosoma*, as in the case of coinfection with *E. histolytica*. Finally, the severity of the subsequent coinfection could also be due to the absence of a strong immune response in the host due to an ongoing immune response to *Schistosoma*, as in coinfection with *E. histolytica*, *Leishmania* or *Plasmodium*. As many of these studies suggest, the subsequent infection may progress or resist standard treatment if the underlying coinfection with *Schistosoma* is not properly diagnosed and treated.

Only 3 of the 18 *Schistosoma* coinfection interactions reviewed herein have a considerable body of literature, that is, between 16 and 32 papers per interaction. These *Schistosoma* interactions involve *Plasmodium*, *Salmonella* and *Fasciola*. The other *Schistosoma* coinfections we reviewed have a much smaller body of literature (between three and nine papers per

interaction). Because of the common occurrence of *Schistosoma* with *Mycobacteria*, *Leishmania*, *Staphylococcus*, *Necator* and *Strongyloides*, additional work is needed on coinfection with *Schistosoma* and these genera. Finally, future studies should take into consideration the factors mentioned in the first paragraph of Section 1.8.

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