

HTLV-I and *Strongyloides* in Australia: The worm lurking beneath

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Abstract

Strongyloidiasis and HTLV-I (human T-lymphotropic virus-1) are important infections that are endemic in many countries around the world with an estimated 370 million infected with *Strongyloides stercoralis* alone, and 5–10 million with HTLV-I. Co-infections with these pathogens are associated with significant morbidity and can be fatal. HTLV-I infects T-cells thus causing dysregulation of the immune system which has been linked to dissemination and hyperinfection of *S. stercoralis* leading to bacterial sepsis which can result in death. Both of these pathogens are endemic in Australia primarily in remote communities in Queensland, the Northern Territory, and Western Australia. Other cases in Australia have occurred in immigrants and refugees, returned travellers, and Australian Defence Force personnel.

HTLV-I infection is lifelong with no known cure. Strongyloidiasis is a long-term chronic disease that can remain latent for decades, as shown by infections diagnosed in prisoners of war from World War II and the Vietnam War testing positive decades after they returned from these conflicts. This review aims to shed light on concomitant infections of HTLV-I with *S. stercoralis* primarily in Australia but in the global context as well.



1. Introduction

Strongyloidiasis and HTLV-I (human T-lymphotropic/leukaemia virus-I) infection cause important diseases that are endemic in many countries around the world. Both pathogens are endemic in Aboriginal people (Cassar et al., 2013) but are often neglected causes of infectious disease in Australia. However, there are indications that the serological prevalence of HTLV-I is particularly high in Central Australia, with an estimate of 40% of individuals infected in one community (Einsiedel et al., 2016c). The prevalence of *S. stercoralis* in northern and Central Australia is also high with estimates of seropositivity ranging from 10% to 60% (Table 1) (Einsiedel et al., 2016c; Einsiedel and Woodman, 2010; Flannery and White, 1993; Sampson et al., 2003; Shield et al., 2015). Each can have severe consequences on the health of infected persons; concomitant infections can lead to dangerous disease sequelae and death.

Strongyloidiasis is caused by parasitic nematodes (roundworms) of the genus *Strongyloides* and is considered to be one of the most neglected

Table 1 HTLV-I and *Strongyloides stercoralis* infections in Australia from 1976 to 2020.

Years sampled	Refs.	Status	Age	Country of origin/ geographical location	Parasite species	Parasite prev.	HTLV-I prev.	Clinical associations	Methods	Study type
	Zubrinich et al. (2019)	Immigrants	28, 35, 50, 64	Vietnam (1), India (1), Fiji (1), Japan (1)	<i>S. stercoralis</i>	100% (<i>n</i> = 4)		Urticaria	<i>Strongyloides</i> : ELISA (IgG), serology, stool microscopy	Case studies
	Wilson and Fearon (2019)	Resident (non-Indigenous)	12	Australia (NT, Alice Springs)	<i>S. stercoralis</i>	Single patient		Tiredness, pharyngitis, poor appetite, abdominal discomfort, rash	<i>Strongyloides</i> : ELISA (IgG)	Case study
1999–2016	Smith et al. (2019)	Residents		Australia (FNQ)	<i>S. stercoralis</i> <i>S. scabiei</i>	0.24% (1/409) 3% (14/409)	0.98% (4/409)		<i>Strongyloides</i> : Not stated <i>HTLV-I</i> : PA [Serodia], EIA [Murex], CMIA [Abbott]	Hospital case review
1994–1996	Shield et al. (2015)	Residents (Indigenous)	Median 11	Australia (NT, North-Eastern Arnhem land)	<i>Toxocara</i> sp. <i>S. stercoralis</i> <i>S. stercoralis</i> <i>T. trichiura</i> Hookworm <i>Entamoeba</i> spp. <i>Giardia duodenalis</i> <i>Hymenolepis nana</i>	20.51% (8/39) 28.21% (11/39) 18.28% (70/383) 84.86% (325/383) 33.94% (130/383) 31.85% (12/383) 9.40% (36/383) 18.02% (69/383)		<i>Strongyloides</i> : ELISA (IgG) ELISA (IgG) Formol-ether Formol-ether Formol-ether Formol-ether Formol-ether	Survey	
1986 1986 1986 1986 1990 1999	Sampson et al. (2003)	Residents (Indigenous)		Australia (WA, Kimberley) Beagle Bay Lombardina Looma One Arm Point Kalumburu Nilliluna Kalumburu	<i>S. stercoralis</i>	17.8 (5/27) 10% (3/30) 58% (33/57) 4.5% (3/66) 5% (2/40) 37% (36/97) 11.4% (26/228)			<i>Strongyloides</i> : ELISA	Sero-survey

Continued

Table 1 HTLV-I and *Strongyloides stercoralis* infections in Australia from 1976 to 2020.—cont'd

Years sampled	Refs.	Status	Age	Country of origin/ geographical location	Parasite species	Parasite prev.	HTLV-I prev.	Clinical associations	Methods	Study type
1982–1983	Sampson and Grove (1987)	Immigrants	1–69	Vietnam	<i>S. stercoralis</i> <i>T. trichiura</i> <i>Giardia</i> spp. Hookworm <i>A. lumbricoides</i> <i>Hymenopolis nana</i> <i>Opisthorchis</i> / <i>Clonorchis</i> sp. <i>Eosentomon nudilabratum</i> <i>Evaniella erythraspis</i>	1.34% (27/2012) 3.63% (73/2012) 1.79% (36/2012) 2.09% (42/2012) 1.34% (27/2012) 0.45% (9/2012) 0.2% (4/2012) 0.05% (1/2012) 0.05% (1/2012)			<i>Strongyloides</i> : Serology, stool examination	Immigrant arrival survey
2014	Robertson et al. (2017)	Resident	0–97	Australia (North Queensland)	<i>S. stercoralis</i>	6.04% (42/695)			<i>Strongyloides</i> : qPCR, nested cPCR	Hospital based
2000–2002	Rice et al. (2003)	Refugees	0–17	East Africa	<i>S. stercoralis</i> Intestinal parasites	11.28% (15/133) [14 equivocal] 50% (66/133)			<i>Strongyloides</i> : Serology Stool microscopy	Hospital lab based
1993	Reynoldson et al. (1997)	Residents (Indigenous)		Australia (WA, Kimberley region)	<i>S. stercoralis</i> <i>Giardia duodenalis</i> <i>Entamoeba coli</i> <i>Hymenolepis nana</i> Hookworm <i>E. vermicularis</i> <i>T. trichiura</i>	1.9% (2/108) 39.8% (43/108) 40.7% (44/108) 54.6% (59/108) 30.6% (33/108) 6.5% (7/108) 2.8% (3/108)			<i>Strongyloides</i> : Zinc flotation, Kato-Katz	Drug efficacy trial
Served 1962–1975 2010	Rahmanian et al. (2015)	ADF ¹ veterans (served 1962–1995)		Vietnam (1962–1975)	<i>S. stercoralis</i>	11.6% (29/249)			<i>Strongyloides</i> : ELISA, stool microscopy (paste and concentration)	Veteran cohort
1972–1991	Prociv and Luke (1993)	Resident (Indigenous)		Australia (QLD, Torres Strait)	<i>S. stercoralis</i>	1.97% (633/32,145)			<i>Strongyloides</i> : Stool microscopy	Community survey

1972–1973	QLD DOH (1965) and Prociv and Luke (1993)	Residents (Indigenous)		Australia (QLD)	<i>S. stercoralis</i>	0% (0/857)		<i>Strongyloides</i> : Formol–ether concentration	Community surveys
1973–1974						3.5% (58/1654)			
1975–1976						7.6% (163/2133)			
1972–1975						2.0% (57/2819)			
1979–1980						3.0% (53/1792)			
1980–1981						2.0% (48/2394)			
1981–1982						1.0% (21/2099)			
1982–1983						1.2% (25/2065)			
1983–1984						<1% (?/2354)			
1984–1985						1–5% (?/2334)			
1985–1986						2–8% (?/1853)			
1986–1987						1.0% (?/2083)			
1985	Prociv and Adkins (1987)	Immigrant		Kampuchea (now Cambodia)	<i>S. stercoralis</i>	Single patient	Weakness, pneumonia, septicaemia	<i>Strongyloides</i> : Autopsy, various tissues	Case study
	Potter et al. (2003)	Resident (Indigenous)	18	Australia (NT, Arnhem land)	<i>S. stercoralis</i>	Single patient	Diarrhoea, abdominal pain, anorexia	<i>Strongyloides</i> : Stool microscopy	Case study
2006–2009	Paxton et al. (2012)	Refugees		Myanmar	<i>S. stercoralis</i> <i>Schistosoma</i> spp. “Faecal parasites”	20.8% (202/973) 7.0% (80/1136) 43.4% (446/1027)		<i>Strongyloides</i> : Serology Faecal examination (unclear)	Retrospective pathology audit
2006–2007	Pattison and Speare (2008)	RAMSI personnel	23–56	Solomon Islands	<i>S. stercoralis</i>	100% ($n = 14$)* ^b	Rash, epigastric pain, diarrhoea, urticaria	<i>Strongyloides</i> : Faecal microscopy, ELISA	Retrospective review positive cases
1980	Oliver et al. (1989)	POW		Timor, Java, Singapore, Burma–Thailand, Japan	<i>S. stercoralis</i>	17.0% (26/150)	Rash, eosinophilia	<i>Strongyloides</i> : Stool culture	Survey former POWs

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Table 1 HTLV-I and *Strongyloides stercoralis* infections in Australia from 1976 to 2020.—cont'd

Years sampled	Refs.	Status	Age	Country of origin/ geographical location	Parasite species	Parasite prev.	HTLV-I prev.	Clinical associations	Methods	Study type
2013–2014	Ngo et al. (2018)	Refugees		Iraq, Iran, Syria, Afghanistan, Pakistan, Tibet, India, Myanmar (Burma), Egypt, Buhtan, Sri Lanka, Sudan, Lebanon, China, Nepal, DR Congo, Somalia, Eritrea	<i>S. stercoralis</i>	4.1% (136/3307) positive 2.2% (73/3307) equivocal			<i>Strongyloides</i> : ELISA (IgG)	Entry survey
2000–2001	Mukerjee et al. (2003)	ADF ^a , immigrant	65, 76	New Guinea (1), Lebanon (1)	<i>S. stercoralis</i>	<i>n</i> = 2		Rash, diarrhoea, gastric pain, cough	<i>Strongyloides</i> : Serology	Case studies
2010–2011	Mounsey et al. (2014)	Residents (Indigenous)		Australia (NT, East Arnhem land)	<i>S. stercoralis</i>	16.5% (<i>n</i> = 124) pretreatment 12% (<i>n</i> = 30) posttreatment			ELISA, DBS- ELISA	New diagnostic screen
1988–1991	Meloni et al. (1993)	Residents (Indigenous)	0–80	Australia (WA, Kimberley region)	<i>S. stercoralis</i> <i>Giardia duodenalis</i> <i>Hymenolepis nana</i> <i>Entamoeba coli</i> <i>A. duodenale</i> <i>Peridimenaeus</i> <i>orbitospinus</i> <i>Chilomastix mesnili</i> <i>Eobolus</i> <i>pontarpioides</i> <i>Sarcocystis</i> spp. <i>T. trichiura</i> <i>E. vermicularis</i> <i>Cytoisospa belli</i>	0.26% (1/385) 30.9% (119/385) 20.5% (79/385) 13.0% (50/385) 1.3% (5/385) 1.0% (4/385) 0.52% (2/385) 0.52% (2/385) 0.52% (2/385) 0.26% (1/385) 0.26% (1/385) 0.26% (1/385)			<i>Strongyloides</i> : Direct stool microscopy, zinc sulphate flotation method	Community survey
	Lim and Biggs (2001)	Immigrant	50	Laos	<i>S. stercoralis</i>	Single patient		Pruritic rash	<i>Strongyloides</i> : Larvae in sputum	Case study

	Konecny et al. (2018)	Resident	27	Australia (NSW/ Central Australia)	<i>S. stercoralis</i>	Single patient	Diarrhoea, weight loss	<i>Strongyloides</i> : Skin & Ileal biopsy, bronchioalveolar lavage	Case study
1987	Kennedy et al. (1989)	POW	65	Burma-Thailand	<i>S. stercoralis</i>	Single patient		<i>Strongyloides</i> : Jejunum biopsy	
1994–1996	Holt et al. (2017b) and Kearns et al. (2015, 2017)	Residents (Indigenous)		Australia (NT, Arnhem land)	<i>S. stercoralis</i> Hookworm <i>Hymenolepis nana</i> <i>Trichuris trichiura</i>	13.1% (11/84); 4.7% (4/85) 13.1% (11/84); 1.2% (1/85) 23.8% (20/84); 22.4% (19/85) 67.9% (57/84); 48.2% (41/85)		<i>Strongyloides</i> : Direct faecal smear microscopy Agar plate culture PCR, serology	Community MDA survey
2010–2011		Residents (Indigenous)		Australia (Arnhem land)	<i>S. stercoralis</i> <i>S. scabiei</i>	21.39% (175/818) [Baseline] 11.91% (109/915) [12 months]		<i>Strongyloides</i> : ELISA (IgG), agar plate, direct microscopy	Population survey and MDA
1973–1978	Jones (1980)	Residents (Indigenous)		Australia (WA, West Kimberley, Pilbara, Northern)	<i>S. stercoralis</i> <i>Entamoeba coli</i> <i>Giardia duodenalis</i> <i>E. vermicularis</i> <i>Ancylostoma</i> spp. <i>Trichuris trichiura</i> <i>Hymenolepis nana</i> <i>Hymenolepis</i> <i>diminuta</i>	2.0% (33/1683) 0.12% (2/1683) 15.2% (256/1683) 1.13% (19/1683) 5.85% (98/1683) 0.06 (1/1683) 20.4% (343/1683) 0.06% (1/1683)		<i>Strongyloides</i> : Formol-ether sedimentation	Medical audits
1994	Heath et al. (1996)	Returned traveller	54	Fiji, Noumea	<i>S. stercoralis</i>	Single patient	HIV co-infection Urticarial rash, epigastric pain	<i>Strongyloides</i> : Sputum, ELISA, stool microscopy	Case study
1994–1999	Healey and Selva-Nayagam (2001)	Residents (6 Indigenous)		Australia (NT, Darwin)	<i>S. stercoralis</i> <i>S. scabiei</i>	33.33% (2/6)		<i>Strongyloides</i> : Stool microscopy Skin scrapings	Retrospective hospital review

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Table 1 HTLV-I and *Strongyloides stercoralis* infections in Australia from 1976 to 2020.—cont'd

Years sampled	Refs.	Status	Age	Country of origin/ geographical location	Parasite species	Parasite prev.	HTLV-I prev.	Clinical associations	Methods	Study type
2012–2013	Hays et al. (2015, 2017a, b)	Residents (Indigenous)		Australia (WA, Kimberley region)	<i>S. stercoralis</i>	35.52% (92/259) [baseline] 13.39% (32/239) [6 months] 5.78% (12/207) [3 years]			<i>Strongyloides</i> : ELISA (IgG)	3-year cohort study/drug efficacy trial
1990–2014	Gurry et al. (2015)	Refugees, Immigrants		Various	<i>S. stercoralis</i> <i>Schistosoma</i> spp.	8.4% (7/83) 8.6% (5/58)			<i>Strongyloides</i> : ELISA (IgG)	HIV cohort
	Grove (1980)	POW		SEA	<i>S. stercoralis</i>	27.5% (44/160)		Urticaria, larval currens, abdominal pain, diarrhoea, weight loss	<i>Strongyloides</i> : String test, stool microscopy, stool culture	Ex POWs 34–37 years ter
	Grant and Tiong (2018)	Immigrant	78	Australia (Vietnam)	<i>S. stercoralis</i>	Single patient		Abdominal pain	<i>Strongyloides</i> : Biopsy small bowel	Case study
1984–1985	Gracey et al. (1992)	Resident (Indigenous)		Australia (Kimberley)	<i>Strongyloides</i> spp.	4.08% (2/49)			<i>Strongyloides</i> : Formalin–ethyl acetate concentration	Prospective in remote community
2015	Fraser (2019)	Resident (Indigenous)	71	Australia (NSW, north-western/mid North coast)	<i>S. stercoralis</i>	Single patient		Tiredness, lethargy. Patient treated for ovarian cancer	<i>Strongyloides</i> : Serology	Case report
1978	Ford et al. (1981)	Immigrant	60	Burma (Myanmar)	<i>S. stercoralis</i>	Single patient		Wheezing, cough, fever	<i>Strongyloides</i> : Sputum, stool microscopy	Case report
1986; 1976–1990	Flannery and White (1993)	Residents (Indigenous)		Australia (Arnhem land, Donydji, Yirrkala)	<i>S. stercoralis</i>	41.38% (12/29) 59.6% (245/411)			<i>Strongyloides</i> : stool serology	Cross sectional survey
1991–1992	Fisher et al. (1993)	Residents (64 Ss + ve Indigenous)	0–66	Australia (NT, Darwin)	<i>S. stercoralis</i> <i>T. trichiura</i> Hookworm <i>Giardia duodenalis</i>	33.17% (68/205) 45.37% (93/205) 22.93% (47/205) 21.20% (45/205)			<i>Strongyloides</i> : Direct stool microscopy, formol–ether concentration	Retrospective review hospital cases

2000–2006	Einsiedel and Fernandes (2008)	Residents (Indigenous)		Australia (NT, Alice Springs)	<i>S. stercoralis</i>	100% ($n=18$)* ^b	7 positive, 7 not determined, 4 negative	Abdominal pain, cough, vomiting, chest pain, diarrhoea, pruritus, wheeze, dyspnea	<i>Strongyloides</i> : Serology, stool microscopy <i>HTLV-I</i> : Serology (unclear)	Retrospective review hospital cases
1998–2005	Einsiedel and Spelman (2006)	Immigrants (2–52 years after resettlement)	20–88	Fiji (1), SEA (5), China (1), Sri Lanka (1), India (2), Seychelles (2), Ethiopia (2), Russia (1), Italy (1), Greece (1)	<i>S. stercoralis</i>	100% ($n=17$) ^b		Wheeze, dyspnea, eosinophilia, rash, gastrointestinal symptoms	<i>Strongyloides</i> : Faecal microscopy, harada culture, EI	Retrospective review
		Returned travellers	25–61	Papua New Guinea (1), Vanuatu (1), SEA (7), Africa (2)	<i>S. stercoralis</i>	100% ($n=11$)* ^b				
2008–2013	Einsiedel et al. (2018)	Residents (Indigenous)		Australia (NT, Alice Springs)	<i>S. stercoralis</i>	25% (180/721) [111 HTLV-I negative; 69 HTLV-I positive]	36.5% (307/840)	Bronchiectasis	<i>Strongyloides</i> : Serology <i>HTLV-I</i> : EI Murex, PA Serodia, WB, PCR	Hospital-based prospective cohort
2014–2015	Einsiedel et al. (2016c)	Residents (Indigenous)	1 > 35	Australia (NT, remote community)	<i>S. stercoralis</i>	13.89% (10/72)	4.3% (1/23) [children] 40.5% (30/74) [adults]	Bronchiectasis, cough, diarrhoea	<i>Strongyloides</i> : Serology <i>HTLV-I</i> : EI [Murex], PA [Serodia], WB, PCR	Community survey
2008–2009	Einsiedel et al. (2016a)	Residents (Indigenous)	>15	Australia (Alice Springs)	<i>S. stercoralis</i>	18.3% (11/61) + 10 equivocal	$n=74$		<i>HTLV-I</i> : Western blot	Targeted cohort
2009	Einsiedel et al. (2013)	Resident (Indigenous)	39	Australia (NT, Alice Springs)	<i>S. stercoralis</i>	1	1	Infective dermatitis	<i>Strongyloides</i> : Serology <i>HTLV-I</i> : WB	Case study

Continued

Table 1 HTLV-I and *Strongyloides stercoralis* infections in Australia from 1976 to 2020.—cont'd

Years sampled	Refs.	Status	Age	Country of origin/ geographical location	Parasite species	Parasite prev.	HTLV-I prev.	Clinical associations	Methods	Study type
2000–2013	Einsiedel et al. (2016b)	Resident (Indigenous)	40.9 ± 17.3	Australia (NT, Alice Springs)			33.6% (635/1889)		HTLV-I: WB	Hospital cohort
2001–2005	Einsiedel and Woodman (2010)	Residents (Indigenous)		Australia (NT, Alice Springs)	<i>S. stercoralis</i>	35.4% (73/206)	43.0% (116/270)		<i>Strongyloides</i> : Serology HTLV-I: WB	Retrospective review
2000–2010	Einsiedel et al. (2014b)	Residents (Indigenous)	>15	Australia (Alice Springs)	<i>S. stercoralis</i> <i>S. scabiei</i>	23.9% (269/1126) (111 HTLV-I +) 14.2% (152/1451) (71 HTLV-I +)	38.7% (624/1614)		<i>Strongyloides</i> : Serology, stool microscopy HTLV-I: EI Murex, PA Serodia, WB, PCR	Retrospective review
7–20 years after resettlement	de Silva et al. (2002)	Immigrant	18–82	Lao	<i>S. stercoralis</i>	24.21% (<i>n</i> = 95)			<i>Strongyloides</i> : Stool microscopy, ELISA	GP survey
2004–2008	Chaves et al. (2009)	Immigrant	16–86	Burma (Myanmar)	<i>S. stercoralis</i>	26% (<i>n</i> = 156)			<i>Strongyloides</i> : Serology	Retrospective cohort study
	Chan et al. (2018)	Immigrant	72	Australia (Vietnam)	<i>S. stercoralis</i>	1			<i>Strongyloides</i> : Laproscopic mesenteric biopsy	Case study
2000, 2002	Caruana et al. (2006)	Immigrant	>15	East Africa Cambodia	<i>S. stercoralis</i> <i>T. trichiura</i> <i>G. duodenalis</i> <i>E. histolytica</i> <i>Holtbyrnia</i> <i>cyanoccephala</i> <i>D. fragilis</i>	0% (0/117) 4.27% (5/117) 5.13% (6/117) 3.42% (4/117) 0.85% (1/117) 0.85% (1/117)			<i>Strongyloides</i> : SAAFF [Para Pak], ELISA (IgG)	Cross-sectional survey of recent immigrants
				Cambodia	<i>S. stercoralis</i> Hookworm	4.9% (10/204) 1.95% (4/204)				

2005–2011	Boan et al. (2017)	Resident (Indigenous)		Australia (WA, Perth)	<i>S. stercoralis</i>	25% (3/12)	0% (0/3)	<i>Strongyloides</i> : Unclear <i>HTLV-1</i> : Unclear	Retrospective cohort
2002 2–28 years after immigrating	Biggs et al. (2009)	Immigrant	16–78 (Ss +)	Cambodia	<i>S. stercoralis</i>	35.04% (82/234)		<i>Strongyloides</i> : ELISA, faecal microscopy	Health assessment
	Best et al. (1976)	Residents (Indigenous)	5–9	Australia (QLD, Cape York Peninsula, Kowanyama)	<i>S. stercoralis</i> <i>G. duodenalis</i> <i>T. trichiura</i> <i>H. nana</i> <i>E. histolytica</i>	9.68% (6/62) 33.87% (21/62) 38.71% (24/62) 27.42% (17/62) 8.06% (5/62)		<i>Strongyloides</i> : Wet mounts, faecal smears, zinc concentration	Community survey
1996; 2004; 2005	Miller et al. (2018)	Residents (Indigenous)		Australia (QLD, Woorabinda)	<i>S. stercoralis</i>	5% (7/139) 12% (113/944) 30% (260/867); (26/129)		<i>Strongyloides</i> : Faecal examination Serology	Hospital retrospective, community study
1969	Walker-Smith et al. (1969)	Resident (Indigenous)	6 months	Australia (NSW, Bowraville)	<i>S. stercoralis</i>	1	Bowel obstruction	<i>Strongyloides</i> : Stool examination	Case study
2004–2012	Soulsby et al. (2012)	Resident		Australia (Alice Springs)	<i>S. stercoralis</i>	4	Urticaria, rash, diarrhoea, a cough, wheezing, epigastric pain, abdominal pain, nausea	<i>Strongyloides</i> : Serology (unclear)	Case studies
1985–1989	Yiannakou et al. (1990)	Resident (9 Indigenous) Refugee POW		Australia (QLD, Townsville, Palm Island, Charters towers) Vietnam	<i>S. stercoralis</i>	11 (Resident) 2 (Refugee) 1 (POW)	Diarrhoea, rash, vomiting, pruritis	<i>Strongyloides</i> : Stool examination	Retrospective review
1996–2002	Page et al. (2006)	Residents (Indigenous)		Australia (NT, Arnhem land)	<i>S. stercoralis</i>	79		<i>Strongyloides</i> : Serology	Serological study, targeted cohort

Continued

Table 1 HTLV-I and *Strongyloides stercoralis* infections in Australia from 1976 to 2020.—cont'd

Years sampled	Refs.	Status	Age	Country of origin/ geographical location	Parasite species	Parasite prev.	HTLV-I prev.	Clinical associations	Methods	Study type
2002–2012	Mayer–Coverdale et al. (2017)	Residents (388 Ss + ve Indigenous)	0 > 80	Australia (NT, Katherine, Tennant Creek, Alice Springs, Nhulunbuy)	<i>S. stercoralis</i>	1.7% (389/22,892)			<i>Strongyloides</i> : Formalin–ethyl acetate concentration	Retrospective
2002–2005	Bradbury and Thomas (2006)	Refugees		Australia (Sudan, Sierra Leone)	<i>S. stercoralis</i>	20% (<i>n</i> = 2686)			<i>Strongyloides</i> : SAF faecal concentration	Hospital based screening
1977 1984/86	May et al. (1990)	Residents (Indigenous)	0 > 60	Australia (WA, Fitzroy – crossing (FC); central Australia (CA))	–	–	15.73% (28/178) FC 1977 13.89% (66/475) CA 1977 33.75% (27/80) CA 1984/86		<i>HTLV-I</i> : WB, ELISA	Community survey, hospital testing
1988	Bastian et al. (1993a, b, c)	Residents (Indigenous)		Australia (Darwin)	–	–	0.036% (4/11,121)		<i>HTLV-I</i> : PA [Serodia], WB	Blood donors
	Chew et al. (2018)	Residents (Indigenous)	39, 48	Australia (Central Australia/Alice Springs)	–		2	Uveitis	<i>HTLV-I</i> : Serology	Case studies
2000–2006	Einsiedel et al. (2012)	Residents (Indigenous)		Australia (Alice Springs)	<i>S. stercoralis</i>	1	58.4% (89/52)	Bronchiectasis	<i>HTLV-I</i> : PA [Serodia], EI [Murex], WB	Retrospective cohort study
2010	Faull and Panegyres (2014)	Residents (non-indigenous)	41	Australia (WA, Great Sandy Desert)	–		1	HAM/TSP	<i>HTLV-I</i>	Case study
2008–2015	Marr et al. (2017)	Residents	6 months to 2 years	Australia (NT)	–	–	15.94% (774/4857)	Hep B	<i>HTLV-I</i> : PA [Serodia], CMIA [Abbott], WB	Retrospective hospital cohort
	Menz et al. (2018)	Residents (Indigenous)		Australia (Adelaide)	–		1	Infective dermatitis	<i>HTLV-I</i> : WB	Case study

2004–2005	Steinfert et al. (2008)	Residents (59/61 Indigenous)		Australia (Alice Springs)	–		72% (18/25)	Bronchiectasis	HTLV-I: Serology	Retrospective hospital based
2000–2009	Davies et al. (2012)	Residents (371 Indigenous)		Australia (NT, Darwin, Arnhem land)	–		2.3% (10/440)		HTLV-I: EI [Murex], PA [Serodia], CMIA [Abbott]	Retrospective pathology services
2008–2011	Grivas et al. (2014)	Residents (367 Indigenous)		Australia (NT)	–		10.35% (368/3555)		HTLV-I: PA [Serodia], CMIA [Abbott]	Retrospective pathology services
2003–2013	Robertson et al. (2014)	Residents		Australia (QLD), Arukun (AK), Gununa/Mornington Island (GMI)	<i>S. stercoralis</i>	–	1.60% (20/1247) AK 3.45% (37/1078) GMI		Formalin-ethyl acetate microscopy	Retrospective pathology services
2014	Nayar et al. (2018)	Residents (Indigenous)	50	Australia (Alice Springs)	–		1	Bladder dysfunction	HTLV-I: Serology	Case study
	Rajabalendran et al. (1993)	Residents (Indigenous)	31	Australia (Alice Springs)	–		1	Progressive weakness in legs	HTLV-I: PA [Serodia], WB, EI	Case study
	Nicholson et al. (1992) and Wylie and Thomson (1992)	Residents		Australia	–		0.36% (4/11, 114)		HTLV-I: WB	Blood donors, other diseases, drug users
	Kirkland et al. (1991)	Residents (Indigenous)	44	Australia (Central Australia)	–		1		HTLV-I: Unclear	Case study
2004–2014	Styles et al. (2017)	Residents		Australia (Blood bank)	–	–	3:1,000,000	–	HTLV-I: Serology	Blood donors
	Mollison et al. (1993)	Residents		Australia (NT)	<i>S. scabiei</i>	58.33% (14/24)	<i>n</i> = 24		HTLV-I:	Community

Continued

Table 1 HTLV-I and *Strongyloides stercoralis* infections in Australia from 1976 to 2020.—cont'd

Years sampled	Refs.	Status	Age	Country of origin/ geographical location	Parasite species	Parasite prev.	HTLV-I prev.	Clinical associations	Methods	Study type
1992–1993	Mollison (1994)	Residents (Indigenous) (caucasian)		Australia (NT)	<i>S. scabiei</i>	14.81% (8/54)	40.74% (22/54) 0% (0/15)	Bronchiectasis	HTLV-I: PA [Serodia], WB	Community
2008–2018	Hung et al. (2019)	Residents		Australia (NT)	<i>S. stercoralis</i> <i>Hymenolepis nana</i> Hookworm <i>Trichuris trichiura</i>	0.48% (240/49,679) 0.82% (406/49,679) 0.09% (44/49,679) 0.41% (204/49,679)			<i>Strongyloides</i> : Faecal wet mount microscopy, faecal concentration	Retrospective
2018	Paltridge et al. (2019)	Residents (2 Ss + ve Indigenous)	Mean 28.2	Australia (FNQ, Cairns)	<i>S. stercoralis</i>	3.33% (2/60)			<i>Strongyloides</i> : ELISA	Prospective hospital based cohort—pregnant women
2000–2018	Paltridge et al. (2020)	Residents	33–62	Australia (FNQ, Cairns)	<i>S. stercoralis</i>	26.6% (645/2429)			<i>Strongyloides</i> : Serology (ELISA, IVD, Bordier)	Retrospective hospital based
2006–2011	Beknazarova et al. (2018) and Eager (2011)	Residents (54 Ss + ve Indigenous)		Australia (FNQ, Kuranda)	<i>S. stercoralis</i>	30.11% (106/352) Indigenous 11.05% (40/362) non-indigenous			<i>Strongyloides</i> : Serology	Medical center
2011	Page (2011)	Resident		Australia (NT, Nhulunbuy)	<i>S. stercoralis</i>	2			<i>Strongyloides</i> : Serology, faecal microscopy	Case study

^aAustralian Defence Force.^bRetrospective review of positive cases.FNQ, Far North Queensland; QLD, Queensland; WA, Western Australia; NT, Northern Territory; NSW, New South Wales; PA, particle agglutination; WB, Western Blot; EI, Immunoassay; ELISA, Enzyme linked Immunosorbant assay; PCR, polymerase chain reaction; CMIA, Chemiluminescent Microparticle Immuno Assay; POW, prisoner of war; ADF, Australian defence forces; Ss, *S. stercoralis*; Ss, *Sarcoptes scabiei*; +ve, positive.

(Olsen et al., 2009) of the neglected tropical diseases (NTDs), as defined by the World Health Organization (WHO, 2019a). Within the NTDs it comes under the umbrella of the soil transmitted helminthiasis (STH) with the main species being *Ascaris lumbricoides* (roundworm), *Trichuris trichiura* (whipworm), and *Ancylostoma* spp. and *Necator americanus* (hookworms). There are two main *Strongyloides* species that cause human infection; *S. stercoralis* and *S. fuelleborni*. *S. fuelleborni* has two distinct subspecies, *S. fuelleborni fuelleborni* and *S. fuelleborni kellyi* (Nutman, 2017; Viney et al., 1991). *S. stercoralis* infections are often overlooked in community-wide studies in endemic areas globally. This is because larvae are excreted intermittently and in low numbers, and are therefore not readily detectable by routine faecal microscopic examination. Worldwide, *Strongyloides* spp. are estimated to infect up to 370 million people, predominantly in socioeconomically disadvantaged communities (Beknazarova et al., 2016; Bisoffi et al., 2013; Olsen et al., 2009). In Australia *S. stercoralis* is the infecting species, based on the criterion that larvae and not eggs are present in fresh faeces of infected people (Best et al., 1976; Einsiedel and Fernandes, 2008; Mayer-Coverdale et al., 2017; Robertson et al., 2017; Sandground, 1925; Viney and Lok, 2007). It has recently been demonstrated that a genetic clade of *S. stercoralis* infecting both dogs and humans exists in Cambodia, Myanmar, and Japan (Jaleta et al., 2017; Nagayasu et al., 2017), suggesting the possibility of zoonotic transmission, while two other clades have thus far only been identified exclusively in dogs; all three clades have been detected in Australia (Barratt et al., 2019; Beknazarova et al., 2019).

S. stercoralis infection in those who are immunocompromised, whether or not this is due to the administration of drugs, can be susceptible to disseminated strongyloidiasis. HTLV-I, which negatively affects the immune system, is an important co-infection leading to increased morbidity in those concomitantly infected with both pathogens (Carvalho and Da Fonseca Porto, 2004).

We review HTLV-I and *S. stercoralis* infections in Australia with reference to the global context of both pathogens; we consider their lifecycles, prevalence among the three primary cohorts identified in Australia (Australian Aboriginals, refugees and immigrants, and returned service personnel and travellers), and options for diagnosis, treatment and control. Where Australian research is lacking, we draw on work carried out in other countries where these two infections are co-endemic.



2. *Strongyloides stercoralis* background

Two species of *Strongyloides* can cause human infection, *S. stercoralis* and *S. fuelleborni* (Nutman, 2017; Viney and Lok, 2007). Infection with *S. fuelleborni* may be caused by two subspecies: *S. f. fuelleborni* and *S. fuelleborni kellyi* (Nutman, 2017; Viney et al., 1991). Human disease caused by *S. stercoralis* and *S. f. fuelleborni* can be zoonotic, with *S. stercoralis* found in canines and felines and *S. f. fuelleborni* in non-human primates (Thanchomnang et al., 2017, 2019; Wulcan et al., 2019). *S. fuelleborni kellyi*, which has been found infecting humans in New Guinea, has no known non-human hosts, although it is still thought to originate from zoonotic sources (Ashford et al., 1992; Kelly et al., 1976). Human infections with the *S. f. fuelleborni* subspecies have been identified in Thailand, India and Africa (Ashford et al., 1992; Barratt et al., 2019; Hasegawa et al., 2016; King and Mascie-Taylor, 2004; Thanchomnang et al., 2017). The genetic determination of *S. f. fuelleborni* in humans from Thailand is based on a short sequence of DNA extracted from faeces and does not align with parasite sequences from the Macaques from which human infections were posited to come from, or other non-human primate sequences available (Thanchomnang et al., 2017). It is possible then that this is an indication of human infection with the subspecies, but not evidence of zoonosis; further in-depth sequencing and comparison of human parasites with those from the infected Macaques would be required to determine whether this indeed constitutes a zoonosis. A recent report of three cases of *S. fuelleborni* infection from Australia was made in error (Barratt et al., 2019; Richard Bradbury, Personal communications). Differentiation of *S. fuelleborni* and *S. stercoralis* is based on morphological differences in the vaginal orientation of free-living females, and the passage of eggs rather than rhabditiform larvae in faeces (Kelly et al., 1976; Speare, 1989) (Fig. 1). *S. f. fuelleborni* and *S. fuelleborni kellyi* can be distinguished by the nature of the peri-vulval cuticle in the free-living female and the position of the phasmidal pore in the free-living male (Kelly et al., 1976; Viney et al., 1991). The most commonly used real-time PCR diagnostic method does not differentiate *S. stercoralis* from *S. fuelleborni* (Verweij et al., 2009).

Recent short-sequence mitochondrial *cox1* genotyping of dogs and human samples identified three separate *S. stercoralis* genotypes split into at least three clades, with two found in infected dogs, and the other present in both dog and human hosts (Beknazarova et al., 2019; Jaleta et al., 2017;

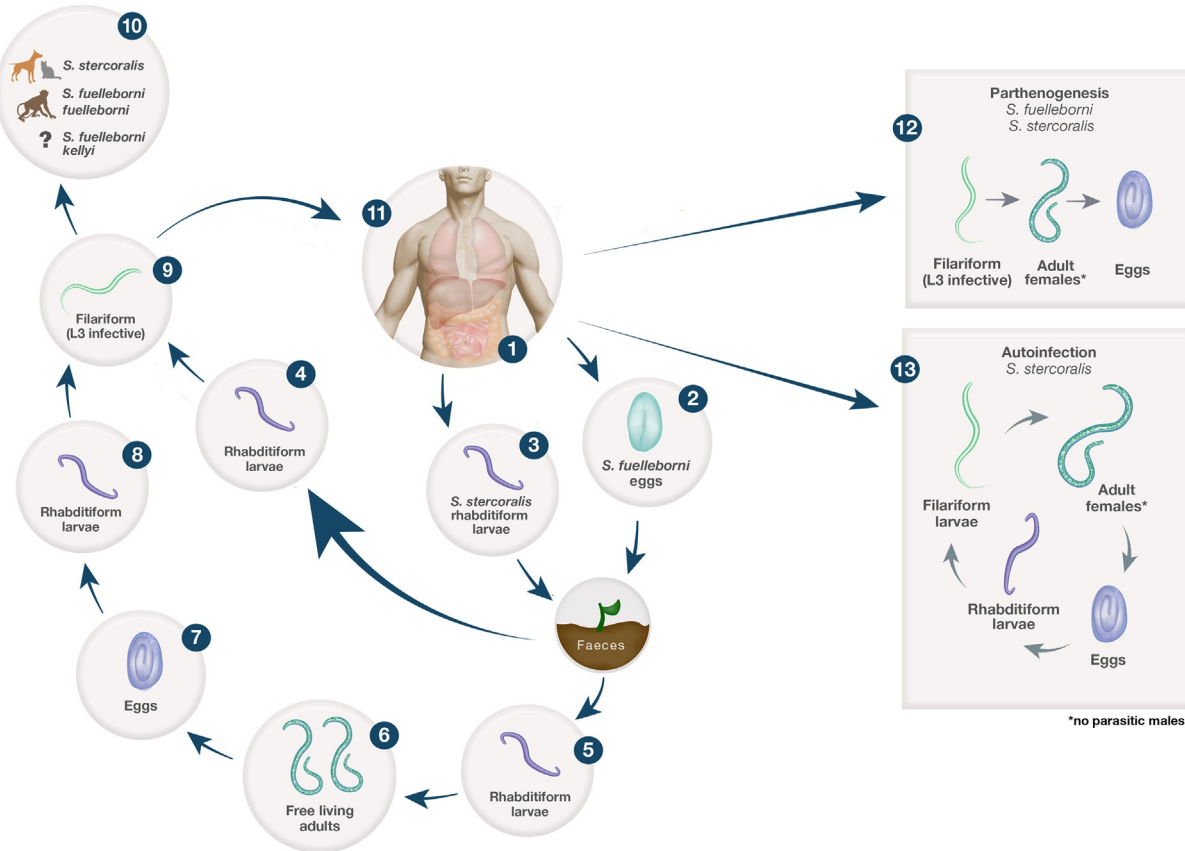


Fig. 1 See figure legend on next page.

Nagayasu et al., 2017). The existence of the dog and human infecting clade suggests a potential role for dogs as a zoonotic reservoir for human infecting genotypes of *S. stercoralis*. Initial work comparing Asian dog and human genotypes from cultured larvae found identical *cox 1* and small subunit rRNA (SSU rRNA) genotypes from both hosts (Jaleta et al., 2017; Nagayasu et al., 2017). Further studies incorporating a next generation sequencing approach identified identical new genotypes of *S. stercoralis* in dogs from remote Australian communities (Barratt et al., 2019; Beknazarova et al., 2019). Genotypes identified from humans and dogs differed when sequences from humans in Australia were aligned; there were several shared single nucleotide polymorphisms (SNPs) in both dogs and humans, although overall sequences were

Fig. 1 Lifecycle of *Strongyloides stercoralis*, *S. fuelleborni fuelleborni*, and *S. fuelleborni kellyi*.

1 Adult female worms live in the small intestine of the host and produce eggs. 2 *S. fuelleborni* eggs are excreted into the environment via the faeces and hatch into rhabditiform larvae. 3 *S. stercoralis* eggs hatch inside the small intestine and rhabditiform larvae are usually excreted into the environment via the faeces. Once in the environment *S. stercoralis* and *S. fuelleborni* 4 rhabditiform larvae can then develop directly into 5 filariform larvae or develop from 5 rhabditiform larvae into 6 free-living adults. This free-living cycle only completes one generation; the first generation filariform larvae cannot become free-living adults and must penetrate a host to continue their lifecycle. The free-living adults reproduce sexually, producing 7 eggs which hatch into 8 rhabditiform larvae which undergo successive moults to become 9 infective filariform larvae. 10 In addition to humans, *S. stercoralis* has previously been found in canids and felids, while *S. fuelleborni fuelleborni* can also infect non-human primates. It is not known if an animal host of *S. fuelleborni kellyi* exists. 11 The filariform larvae directly penetrate the skin of the human or animal host and migrate randomly to the small intestine (Page et al., 2018; Schad, 1989), or they can undergo circulatory-pulmonary-tracheal migration whereby they penetrate the alveolar spaces of the lungs and are coughed up and swallowed. 12 Once in the small intestine they moult twice more into parasitic females (there are no parasitic males) which reproduce via parthenogenesis.

13 *S. stercoralis* eggs hatch into rhabditiform larvae inside the small intestine and can moult into infective filariform larvae in the lower GIT, thereby causing autoinfection. These autoinfective filariform larvae penetrate the intestinal mucosa or skin around the anus and are carried by the circulatory-pulmonary-tracheal route or migrate via other organs. Autoinfection can result in persistent, long-lived infections for decades. It also contributes to hyperinfection, usually seen in immunocompromised individuals, and can result in bacterial sepsis which in severe cases can cause death. The lifecycle of *S. fuelleborni kellyi* is considered to be identical to *S. fuelleborni fuelleborni* except that no zoonotic hosts have been identified for *S. fuelleborni kellyi*.

quite short (217–434bp) (Barratt et al., 2019; Beknazarova et al., 2019) (Supplementary Table 2 in the online version at <https://doi.org/10.1016/bs.apar.2020.11.002>). This was further supported by the recent application of a machine learning based algorithm used to create a maximum likelihood clustered distance tree of the combined sequences of *cox1* and two SSU rRNA targets (Barratt and Sapp, 2020). This approach identified seven distinct genotypic clusters, of which one was only found in dogs, another was skewed towards dog hosts, but did include some human infections. While the other five clusters predominantly contained human samples, dog-infecting isolates were interspersed in these clusters (Barratt and Sapp, 2020). However, it remains possible that the host-specific clustering evident in the above studies is an artefact of limited sampling from a single host in small geographic areas. Wider sampling of both hosts in the same areas is indicated to definitively confirm these data.

In three of these reports, DNA extraction and subsequent sequencing was performed directly from faecal samples collected from the environment. A deficiency of this approach is the fact that no controls were included to exclude possible coprophagia of human faeces by the dogs sampled. Consequently, it is possible that these genotypes represent intestinal passage of *S. stercoralis* DNA after consumption of infected human faeces by the dog hosts (Barratt et al., 2019; Beknazarova et al., 2019). Earlier work with similar findings genotyped individual cultured larvae (Jaleta et al., 2017; Nagayasu et al., 2017), and intestinal passage of viable, intact, human larvae through the dog digestive tract is less likely to occur. Ultimately, the short *cox1* sequences and the limited variability of the SSU RNA targets sequenced in most *S. stercoralis* genotyping studies limits the level of discrimination and prohibits correct phylogeny construction. The limited genotyping data using these targets has, to date, thus provided tangential evidence of a potential *S. stercoralis* transmission cycle between dogs and humans, at least in some Asian and Australian communities, but this hypothesis requires further investigation to provide definitive proof.

Only one study has thus far produced any sequence data for *S. f. kellyi*. Its conclusions, based on a 330bp sequence of the 18s rRNA gene (Genbank accession number [AJ417029](#)), did not support *S. fuelleborni kellyi* as a subspecies of *S. fuelleborni* (Dorris et al., 2002). This short sequence had 100% identity with the same 18s rRNA regions deposited in Genbank of *Strongyloides venezuelensis*, *Strongyloides ransomi*, *Strongyloides vituli* and *Strongyloides cebus*. Moreover, the sequence showed only two base pair difference (both T–A) from *S. fuelleborni* subsp. *fuelleborni* from a Japanese macaque. Overall, the

combined data and the single short read sequence is insufficient to ascribe *S. fuelleborni kellyi* as a new species.

2.1 Lifecycle and disease

The lifecycle of *Strongyloides* spp. is complex and has both a parasitic cycle and a facultative free-living cycle. In contrast to *S. fuelleborni*, *S. stercoralis* can cause autoinfection within the definitive host (Fig. 1) (Page et al., 2018). Autoinfection occurs when the rhabditiform larvae develop directly into infective filariform larvae while still in the host, which can then penetrate the lower gut and migrate to the intestine via other organs, carrying gut bacteria with them. When this process is accelerated in immunocompromised individuals, dissemination to other organs can cause damage and bacterial sepsis leading to death; mortality associated with disseminated strongyloidiasis is high (Basile et al., 2010; Buonfrate et al., 2013; Konecny et al., 2018). Dissemination and hyperinfection are interconnected states that occur due to accelerated autoinfection and are often associated with a decreased immune response due to the effects of drugs/biologics such as corticosteroids and other immunosuppressive therapies, solid organ transplantation, HTLV-I infection, cancer, leukaemia, and old age (Mejia and Nutman, 2012). Weakened immune defences lead to parasite migration and dissemination (Aru et al., 2017). Genta (1992) hypothesized that corticosteroids, as well as affecting the immune response, have a direct effect on *S. stercoralis* larvae, favouring the development of autoinfective larvae in the gut. Recent work using the NSG (NOD (non-obese) diabetic scid gamma) mouse model supports this hypothesis. *S. stercoralis* has a DAF-12 nuclear receptor that regulates parasite development and can be controlled by $\Delta 7$ -dafachronic acid, an endogenous nematode steroid. Methylprednisolone acetate induces and $\Delta 7$ -dafachronic acid suppresses *S. stercoralis* hyperinfection in NSG mice. DAF-12 has the potential to become a novel chemotherapeutic target for treating lethal hyperinfection (Albarqi et al., 2016; Patton et al., 2018).

While free-living adults of *S. stercoralis* only complete one generation before reverting to parasitism (Yamada et al., 1991), it is less straight forward in *S. fuelleborni fuelleborni* and seems to differ depending on the intensity of infection and 'quality' of the faeces, as determined by faecal culture conditions (Hansen et al., 1969). In high intensity infections and under aerobic conditions filariform larvae develop directly from the originally excreted eggs. It is only under semi-anaerobic conditions that adults develop. In lower intensity infections sexual adult forms develop and filariform larvae

are a result of mating between these free-living adults; in very low numbers a second generation of free-living adult females who mate with first generation males and resultant filariform larvae constitute the third generation (Hansen et al., 1969). Most species of *Strongyloides* have an external cycle with only one free-living generation (Viney and Lok, 2007), the exception being *Strongyloides planiceps* where up to nine generations under culture conditions have been reported (Yamada et al., 1991).

As mentioned earlier, there are three possible phases recognized for *S. stercoralis* infection—acute, chronic and hyperinfection/dissemination (Nutman, 2017; Page and Speare, 2016). The acute phase follows initial infection and is relatively short. Once infection is established, there is an autoinfective burst (Schad et al., 1997) and, dependent on the numbers of adult females present, results in increasing numbers of larvae found present in faeces; however, serology by IgG-enzyme-linked immunosorbent assay (IgG-ELISA) may be negative or equivocal during this phase due to a ‘window’ period before antibody levels become elevated (Grove and Northern, 1982; Page and Speare, 2016; Speare and Durrheim, 2004). Symptoms range from mild to severe, possibly depending on the number of larvae causing the initial infection (Freedman, 1991; Page, 2011). Skin manifestations, including larva currens and urticarial rash, may be the only sign of initial infection with *S. stercoralis* (Ly et al., 2003; Smith et al., 1976; von Kuster and Genta, 1988). Infected individuals experience various degrees and combinations of fever, cough, urticaria, epigastric pain, diarrhoea and eosinophilia (Caumes and Keystone, 2011; Pattison and Speare, 2008); gastrointestinal symptoms may be severe (Freedman, 1991; Nutman, 2017; Page, 2011; Pattison and Speare, 2008). The chronic phase can last for years to decades with non-specific and intermittent symptoms (Page and Speare, 2016). Faecal larval output is thought to drop during this phase due to a strong immune response which also leads to an increase in IgG levels at this time (Atkins et al., 1997, 1999; Genta and Lillibridge, 1989; Page and Speare, 2016). Infected individuals may be asymptomatic or experience mild to moderate symptoms, including indigestion, urticaria, pruritus ani, diarrhoea and weight loss, which are sometimes intermittently non-specific (Grove, 1980). In a small number of cases, the disease can progress to the final phase—hyperinfection/disseminated strongyloidiasis—which occurs in immunocompromised individuals. It is characterized by a rapid and exponential increase in parasite numbers, with high larval faecal output. In disseminated Strongyloidiasis, larvae are present throughout the body and in bodily fluids such as sputum as well as in faeces. The reduced immune response includes a reduction in

IgG levels and IgG-ELISA serology may return a negative result (Kearns et al., 2017; Lier et al., 2020; Mascarello et al., 2011; Osiro et al., 2017; Page et al., 2006; Rodriguez et al., 2015). Clinical presentations of hyperinfection/disseminated strongyloidiasis include: severe gastrointestinal symptoms (diarrhoea, epigastric pain, paralytic ileus, and ulcerative enteritis) and signs of malnutrition, hypokalaemia, bacterial meningitis, bacterial sepsis, and multiple end-organ failure as well as other rarer presentations (Byard, 2019; Page and Speare, 2016; Shield and Page, 2008).

In Papua New Guinea (PNG), protein losing enteropathy with ascites, referred to as 'swollen belly syndrome', has previously been reported in infants with very high *S. fuelleborni kellyi* faecal egg counts (Ashford et al., 1992). Symptoms include a distended and swollen abdomen, diarrhoea, respiratory distress, weight loss, hypoproteinaemia, and peripheral oedema (Ashford et al., 1992). There is high mortality with this syndrome. External autoinfection is known to occur in infants when they are cradled on soiled bedding of leaves or cloth used to line string bag carrying cradles (Ashford et al., 1992; Ashford and Barnish, 1989). Due to the high humidity and mist, particularly in mountainous areas of PNG, the cradles are continuously damp, a perfect place for the *S. fuelleborni kellyi* larvae to rapidly develop into infective filariform larvae, allowing for very high infections leading to cases of swollen belly syndrome. Transmammary transmission has been suspected in *S. fuelleborni kellyi* and has been shown to occur in human infections with *S. fuelleborni fuelleborni* in Africa (Brown and Girardeau, 1977); however, despite attempts to find *S. fuelleborni kellyi* larvae in maternal milk (Ashford et al., 1992), there is no evidence of transmammary transmission in humans (Shoop et al., 2002).

2.2 Temperature and other environmental factors

S. stercoralis is not restricted to tropical and subtropical zones, as is evident with the parasite also identified in temperate zones (Beknazarova et al., 2016; Fraser, 2019; Schär et al., 2013). The autoinfective cycle (Fig. 1) enables *S. stercoralis* to maintain an infection without the need to reinfect the host from the external environment; thus the infection is maintained even when the external milieu is unfavourable. Poor hygiene may also allow for person-to-person transmission.

Studies examining the survivability of *S. ratti* larvae at different temperatures showed that at a temperature range of 15–37 °C larvae could survive for up to 24 days, although 22–28 °C is considered optimal (Barrett, 1968).

Similar studies involving *S. fuelleborni* showed optimal development of larvae between 23 and 25 °C; eggs also hatched faster at higher temperatures (23–40 °C) compared to lower temperatures (10–11 °C) where hatching took 26–48 h (Cordi and Otto, 1934). There was no mortality observed at lower temperatures, and further investigation found that higher temperatures (>37 °C) reduced long-term survivability, particularly of filariform larvae. Temperatures of 11–16 °C resulted in slower development but longer life spans (27 days for 53% of larvae) while 0–5 °C was associated with a reduced life span (2 days 24% survivability), and at 23–25 °C the life span was 11 days for just over 50% of larvae tested (Cordi and Otto, 1934). As development is faster at higher temperatures, infective filariform larvae need to infect a new host rapidly. However, in temperate areas the larvae will remain in the soil for a longer time which will impact on control and transmission (Cordi and Otto, 1934). *S. stercoralis* has an optimal temperature range of 26–28 °C for larval development (Sandground, 1925). The short survival time of larvae in the external environment together with the maximum single free-living generation ensures that the free-living stages survive less than a month after faecal contamination of the environment. Transport of faecal samples from remote locations to a central laboratory for routine diagnostic testing of *Strongyloides* at high temperatures or when refrigerated will lead to death of larvae present (Cordi and Otto, 1934). Experiments on resistance of larvae to cold storage subjected 74 infected stool specimens to refrigeration at 4 °C for 24, 48, and 72 h; 48.6%, 28.4% and 23%, respectively, of the specimens retained some viable larvae on subsequent agar plate culture (Ines Ede et al., 2011).

2.3 Diagnosis

The laboratory diagnosis of *S. stercoralis* can be difficult due to often low and intermittent shedding of larvae in stool in chronic strongyloidiasis. The main diagnostic procedures employed for *S. stercoralis* include anti-*Strongyloides* IgG antibody serology and faecal testing. Testing of sputum and duodenal fluid is rarely used. DNA testing of urine and blood is being investigated.

Faecal microscopy by experienced technicians is 100% specific. It has low sensitivity in chronic strongyloidiasis but is useful in both acute strongyloidiasis and hyperinfection where the larval output is high (de Kaminsky, 1993). Faecal parasite concentration methods such as formol-ether, Kato-Katz and FLOTAC also yield poor diagnostic outcomes (Campo Polanco et al., 2014; Knopp et al., 2014; Koga et al., 1990; Requena-Mendez

et al., 2013; Steinmann et al., 2007). Baermann extraction and agar plate copro-culture are the highest sensitivity non-nucleic acid faecal methods currently available (Dreyer et al., 1996; Khieu et al., 2013; Knopp et al., 2014; Steinmann et al., 2007). Most nucleic acid diagnostics to date have focused on testing faeces (Tables 1 and 2). Both the Baermann technique and the agar plate culture method isolate larvae of *S. stercoralis* and require viable larvae in the faecal sample. With the Baermann technique, stool is wrapped in gauze, suspended in a funnel that empties into a flask or a clamped rubber tube, and the funnel is filled with water. The larvae exit the faeces into the water and are collected from the funnel sediment over 24 h. If performed on fresh faeces, this technique will collect L1 and L2 rhabditiform stage larvae (Lima and Delgado, 1961). In the agar plate culture method, stool is placed in the centre of an agar plate which is sealed and incubated at 26–38 °C for ~48 h (Arakaki et al., 1988; Koga et al., 1990). Extended incubation for up to 96 h improves recovery (Ines Ede et al., 2011). The filariform larvae migrate from the stool mass into the outer portion of the agar plate and are recognizable by the characteristic bacterial ‘tracks’ made on the agar surface. The unsealed plate can then be examined under a light microscope for larvae; alternatively, fixative is added to the plate to wash the surface of the plate, the liquid removed and the sediment examined for larvae by microscopy. The Baermann technique is not used for routine diagnosis in Australia, and the agar plate culture is rarely used because of the risk of accidental infection of laboratory staff. For non-nucleic acid faecal techniques, the examination of multiple stool samples markedly improves yield (Dreyer et al., 1996; Hirata et al., 2007; Steinmann et al., 2007).

The main barrier to using molecular diagnostics is the high cost, usually associated with DNA extraction. Stool is a complex source of DNA, containing many potential inhibitors to downstream molecular diagnosis and these need to be removed during the DNA extraction process. Nevertheless, molecular diagnostics provide a highly effective and easily performed approach for the diagnosis of *S. stercoralis* and other parasitic worms (Gordon et al., 2011; Pilotte et al., 2016; Verweij et al., 2009). The method of DNA extraction method may influence the sensitivity of any PCR assay (Sultana et al., 2013). In addition, there may be insufficient parasite DNA for amplification, particularly where there is low larval output in chronic strongyloidiasis. A nucleic acid test for *Strongyloides* has recently been developed in an Australian diagnostics laboratory (Watts et al., 2014, 2019).

Table 2 Co-infections of HTLV-I and *Strongyloides stercoralis* infection world-wide.

Co-morbidity/ HTLV-I disease	HTLV-I prevalence % (p/n)	Parasite prev. % (p/n)	Status or location [#]	Geographical location	Age (years)	Diagnostics	Year	Refs.	Type of study
<i>Parasites:</i> Strongyloides	1	1	Resident	Patagonia (Argentina, Chile)	50	<i>Strongyloides</i> : Bronchoalveolar lavage and duodenal and colonic mucosa biopsies <i>HTLV-I</i> : Serology (unclear)	2017	Hunter et al. (2019)	Case study
<i>Parasites:</i> Strongyloides	2	2	Resident	French West Indies (Martinique)	37, 51	<i>Strongyloides</i> : Baermann <i>HTLV-I</i> : Serology (unclear)	1993–1998	Botterel et al. (1998)	Case study
<i>Parasites:</i> Strongyloides Scabies <i>HTLV-I</i> : ID, HAM/TSP, ATLL, Uveitis	38.7% (624/1614)	23.9% (269/1126) (111 HTLV-I +) 14.2% (152/1451) (71 HTLV-I +)	Residents	Australia (Alice Springs)	>15	<i>Strongyloides</i> : Serology, stool microscopy <i>HTLV-I</i> : EIA Murex, PA Serodia, WB, PCR	2000–2010	Einsiedel et al. (2014b)	Hospital based
<i>Parasites:</i> Strongyloides	36.5% (307/840)	25% (180/721) [111 HTLV-I –; 69 HTLV-I +]	Residents	Australia (Alice Springs)		<i>Strongyloides</i> : Serology <i>HTLV-I</i> : EIA Murex, PA Serodia, WB, PCR	2008–2013	Einsiedel et al. (2018)	Hospital based
<i>Parasites:</i> Strongyloides	<i>n</i> = 74	18.3% (11/61) + 10 equivocal	Residents	Australia (Alice Springs)	>15	<i>Strongyloides</i> : Serology <i>HTLV-I</i> : WB	2008–2009	Einsiedel et al. (2016a)	Targeted cohort
<i>Parasites:</i> Strongyloides	71% (22/37)	54.5% (18/37)	Residents	Japan (Okinawa)	19–91	<i>Strongyloides</i> : Larval detection in sputum, faeces, other samples <i>HTLV-I</i> : Serology (unclear)	1993–2015	Mukaigawara et al. (2018)	Retrospective review, hospital based
<i>Parasites:</i> Strongyloides	1	1	Guinea	France	38	<i>Strongyloides</i> : Stool culture, gastroduodenal biopsy, Serology <i>HTLV-I</i> : Serology (unclear), Cervical biopsy		Schein et al. (2018)	Case study

Continued

Table 2 Co-infections of HTLV-I and *Strongyloides stercoralis* infection world-wide.—cont'd

Co-morbidity/ HTLV-I disease	HTLV-I prevalence % (p/n)	Parasite prev. % (p/n)	Status or location [#]	Geographical location	Age (years)	Diagnostics	Year	Refs.	Type of study
<i>Parasites:</i> Strongyloides	36	2.8% (1/36)	Spain, South America, Africa, Asia	Spain	18–67	<i>Strongyloides</i> : Serology <i>HTLV-I</i> : ELISA IgG, CMIA [Abbott], Ab-capture ELISA test system	2008–2015	Salvador et al. (2017)	Cross sectional study of blood donors
<i>Parasites:</i> Strongyloides	1	1	South America	New York	37	<i>Strongyloides</i> : Gastrointestinal biopsy <i>HTLV-I</i> : Serology (unclear)		Tariq et al. (2017)	Case study
<i>Parasites:</i> Strongyloides <i>HTLV-I</i> : ATLL	1	1	Burkina Faso	France	32	<i>Strongyloides</i> : Gastric fluid examination, duodenal biopsy <i>HTLV-I</i> : Serology (unclear)		Malezieux- Picard et al. (2017)	Case study
<i>Parasites:</i> Strongyloides <i>HTLV-I</i> : ATLL	1	1	Resident	Peru	48	<i>Strongyloides</i> : Eosinophilia, family history, duodenal biopsy <i>HTLV-I</i> : Serology (unclear)		Guevara Miranda et al. (2017)	Case study
<i>Parasites:</i> Strongyloides	7 positive, 7 not determined, 4 negative	18 (9 definitive)	Residents	Australia (Alice Springs)	29–72	<i>Strongyloides</i> : Serology, stool microscopy <i>HTLV-I</i> : Serology (unclear)	2000–2006	Einsiedel and Fernandes (2008)	Retrospective review, Hospital based
<i>Parasites:</i> Strongyloides	4.3% (1/23) [children] 40.5% (30/74) [adults]	13.9% (10/72) [6 HTLV-I +]	Residents	Australia (NT)	1 > 35	<i>Strongyloides</i> : Serology <i>HTLV-I</i> : EIA [Murex], PA [Serodia], WB, PCR	2014–2015	Einsiedel et al. (2016c)	Pilot survey
<i>Parasites:</i> Strongyloides	0% (0/1004) [slum] 0% (0/299) [city]	21.9% (220/1004) [slum] 5.0% (15/299) [city]	Residents	Bangladesh	>15	<i>Strongyloides</i> : ELISA (IgG) <i>HTLV-I</i> : EIA [Murex]		Sultana et al. (2012)	Prevalence survey
<i>Parasites:</i> Strongyloides	1	1	Resident	Japan	58	<i>Strongyloides</i> : Duodenum and jejunum biopsy <i>HTLV-I</i> : Antibody positive		Nakamura et al. (2010)	Case study

<i>Parasites:</i> Strongyloides	40.8% (176/431) [81 Ss +]	<i>n</i> = 717 (total no. Ss +)	Residents	Japan	Mean 62	<i>Strongyloides</i> : Agar plate culture <i>HTLV-I</i> : Unclear	1991–2014	Higashiarakawa et al. (2017)	Targeted Strongyloides cohort, hospital study
<i>Parasites:</i> Strongyloides	1	1		Ghana	34	<i>Strongyloides</i> : O&P (pos), ELISA <i>HTLV-I</i> : Previously diagnosed		Alpern et al. (2017)	Case study
<i>Parasites:</i> Strongyloides	1	1		Guinea	Germany	53	<i>Strongyloides</i> : Stool microscopy <i>HTLV-I</i> : Serology (unclear), PCR	Richter et al. (2005)	case study
<i>Parasites:</i> Strongyloides	1	1		West Indies, Caribbean	UK	59	<i>Strongyloides</i> : Stool microscopy, rectal biopsy <i>HTLV-I</i> : Serology (unclear)	Rahim et al. (2005)	Case study
<i>Parasites:</i> Strongyloides	1	1		Resident	Brazil	27	<i>Strongyloides</i> : Spermatogram (unusual presentation), urine and stool examination <i>HTLV-I</i> : WB, ELISA [Genzyme]	Porto et al. (2005b)	Case study
<i>Parasites:</i> Strongyloides (and other helminths)	–	1.4% (51/3752)		Resident	Dominica		<i>Strongyloides</i> : Faecal examination (wet mounts) <i>HTLV-I</i> : Not identified in this study, study area endemic for HTLV-I	1999 Adedayo and Nasiiri (2004)	Retrospective
<i>Parasites:</i> Strongyloides	1	1		Resident	India	24	<i>Strongyloides</i> : Stool examination, biopsy duodenum <i>HTLV-I</i> : Unclear	Patel et al. (2015)	Case study

Continued

Table 2 Co-infections of HTLV-I and *Strongyloides stercoralis* infection world-wide.—cont'd

Co-morbidity/ HTLV-I disease	HTLV-I prevalence % (p/n)	Parasite prev. % (p/n)	Status or location [#]	Geographical location	Age (years)	Diagnostics	Year	Refs.	Type of study
<i>Parasites:</i> Strongyloides	1	1	Resident	Japan	47	<i>Strongyloides</i> : Duodenal biopsy, stool microscopy <i>HTLV-I</i> : PA, IF		Sato et al. (2003)	Case study
<i>Parasites:</i> Strongyloides, other STH <i>HTLV-I</i> : ID	1	1	Haiti (born)	France	10	<i>Strongyloides</i> : Stool microscopy <i>HTLV-I</i> : WB	1997	Gabet et al. (2003)	Case study
<i>Parasites:</i> Strongyloides, IP	—	4% (708/17,660)	Resident	Guadeloupe		<i>Strongyloides</i> : Baermann, wet mount, Bailerger concentration <i>HTLV-I</i> : Not identified, area endemic for HTLV-I	1991–2003	Nicolas et al. (2006)	Retrospective
<i>Parasites:</i> Strongyloides	1	1	Resident	Japan	75	<i>Strongyloides</i> : Sputum, stool microscopy <i>HTLV-I</i> : Antibody test	2000	Mitsunaga et al. (2003)	Case study
<i>Parasites:</i> Strongyloides	1	1	Resident	Brazil	53	<i>Strongyloides</i> : Gastric biopsy, stool microscopy <i>HTLV-I</i> : ELISA, WB		Lambertucci et al. (2003)	Case study
<i>Parasites:</i> Strongyloides Scabies	22.1% (66/298)	66.7% (18/27) 18.5% (5/27)	Dominica	USA	9–89 Mean 56	<i>Strongyloides</i> : Stool microscopy <i>HTLV-I</i> : ELISA, WB	1995–1999	Adeyayo et al. (2003)	Retrospective, hospital based
<i>Parasites:</i> Strongyloides <i>HTLV-I</i> : TSP, ATLL	1	1	Sierra Leone	USA	32	<i>Strongyloides</i> : unclear <i>HTLV-I</i> : Serology (unclear)		Luca et al. (2003)	Case study
<i>Parasites:</i> Strongyloides	74.47% (35/47)	47	Resident	Peru	(10–)50	<i>Strongyloides</i> : Stool culture <i>HTLV-I</i> : ELISA, WB	1990–1998	Terashima et al. (2002)	Retrospective of previously Ss + individuals

<i>Parasites:</i> Strongyloides	34	$n = 50$	Resident	Japan	30–79	<i>Strongyloides</i> : stool culture <i>HTLV-I</i> : Antibody detection (unclear)	1998–1999	Zaha et al. (2002)	Drug efficacy study
<i>Parasites:</i> Strongyloides	32	$n = 79$	Resident	Japan	65.1 ± 11.6 [M] 66.7 ± 8.73 [F]	<i>Strongyloides</i> : ELISA <i>HTLV-I</i> : PA [Serodia]	1994	Satoh et al. (2002)	Drug efficacy study
<i>Parasites:</i> Strongyloides	1	1	Resident	Dominica (West Indian)	45	<i>Strongyloides</i> : Stool microscopy <i>HTLV-I</i> : WB		Adedayo et al. (2001)	Case study
<i>Parasites:</i> Strongyloides	27	$n = 67$	Resident	Brazil		<i>Strongyloides</i> : Stool microscopy, serology (IgE, IgG), skin test <i>HTLV-I</i> : ELISA, WB		Porto et al. (2001b)	Retrospective previously diagnosed Strongyloides or HTLV-I
<i>Parasites:</i> Strongyloides	119/238	31.1% (37/199)	Resident	Guadeloupe	18–65	<i>Strongyloides</i> : serology (IF) <i>HTLV-I</i> : CMIA [Abbott], WB		Courouble et al. (2000)	Blood donors
<i>Parasites:</i> Strongyloides	$n = 91$ (previously identified) $n = 61$ (healthy)	12.1% (11/91) HTLV-I + 1.6% (1/61) HTLV-I –	Resident	Brazil		<i>Strongyloides</i> : Faecal sedimentation, Baermann, Harada-Mori <i>HTLV-I</i> : ELISA, WB		Chieffi et al. (2000)	Blood donors
<i>Parasites:</i> Strongyloides, Giardia	1	1	Togo (West Africa)	Canada	40	<i>Strongyloides</i> : Duodenal biopsy <i>HTLV-I</i> : Serology (unclear)		Isotalo et al. (2000)	Case study
<i>Parasites:</i> Strongyloides	29.4% (62/211)	$n = 211$	Resident	Japan	38–86	<i>Strongyloides</i> : Formalin-ether concentration, Harada-Mori, agar plate <i>HTLV-I</i> : IA [Serodia]		Toma et al. (2000)	Drug efficacy

Continued

Table 2 Co-infections of HTLV-I and *Strongyloides stercoralis* infection world-wide.—cont'd

Co-morbidity/ HTLV-I disease	HTLV-I prevalence % (p/n)	Parasite prev. % (p/n)	Status or location [#]	Geographical location	Age (years)	Diagnostics	Year	Refs.	Type of study
<i>Parasites:</i> Strongyloides	1	1	Jamaica	USA	40	<i>Strongyloides</i> : Small bowel biopsy <i>HTLV-I</i> : Antibody positive (unclear)		Friedenberg et al. (1999)	Case study
<i>Parasites:</i> Strongyloides <i>HTLV-I</i> : ATLL	58.54% (24/41)	32.35% (11/34)	Resident	Martinique	18–88	<i>Strongyloides</i> : Baermann <i>HTLV-I</i> : ELISA, WB		Agape et al. (1999)	Clinicopathological study
<i>Parasites:</i> Strongyloides	24.04% (25/104)	79.81% (83/104)	Resident	Peru		<i>Strongyloides</i> : Baermann, sputum <i>HTLV-I</i> : ELISA, WB		Gotuzzo et al. (1999)	Retrospective
<i>Parasites:</i> Strongyloides	1	1	Resident	France	58	<i>Strongyloides</i> : Duodenal biopsy <i>HTLV-I</i> : Serology (unclear)		Ribier et al. (1999)	Case study
<i>Parasites:</i> Strongyloides	37.35% (31/83)	69.88% (58/83)	Resident	Brazil		<i>Strongyloides</i> : Faecal microscopy, ELISA, skin test <i>HTLV-I</i> : CMIA [Abbott], WB		Neva et al. (1998)	Targeted cohort
<i>Parasites:</i> Strongyloides	1	1	Resident	Japan	70	<i>Strongyloides</i> : Duodenal biopsy <i>HTLV-I</i> : Serology (unclear)	1994	Nonaka et al. (1998)	Case study
<i>Parasites:</i> Strongyloides	1	1	Resident	Japan	73	<i>Strongyloides</i> : Sputum <i>HTLV-I</i> : Unclear		Oya et al. (1998)	Case study [Article in Japanese, unable to translate]
<i>Parasites:</i> Strongyloides	1	1	Resident	Japan	75	<i>Strongyloides</i> : Stool and sputum smear <i>HTLV-I</i> : Serology (unclear)	1982	Higashiyama et al. (1997)	Case study article in Japanese
<i>Parasites:</i> Strongyloides <i>HTLV-I</i> : ATL	N=38	50% (19/38)	Resident	Martinique		<i>Strongyloides</i> : Baermann <i>HTLV-I</i> : Unclear	1983–1995	Plumelle et al. (1993, 1997)	Retrospective

<i>Parasites:</i> Strongyloides	23.01% (310/1347)	21.90% (295/1347)	Resident	Japan	22–89	<i>Strongyloides</i> : Stool microscopy, Agar plate <i>HTLV-I</i> : PA, ELISA, WB	1992	Hayashi et al. (1997)	Clinical, targeted cohort
<i>Parasites:</i> Strongyloides	43.0% (116/270)	35.4% (73/206)	Residents	Australia (Alice Springs)	Means 44–57	<i>Strongyloides</i> : Serology (unclear) <i>HTLV-I</i> : Serology (unclear)	2001–2005	Einsiedel and Woodman (2010)	Retrospective
<i>Parasites:</i> Strongyloides <i>HTLV-I</i> : ATLL	1	1	Resident	Japan	52	<i>Strongyloides</i> : Unclear, previously diagnosed <i>HTLV-I</i> : Serology (unclear)	1995	Hiroyasu et al. (1996)	Case study
<i>Parasites:</i> Strongyloides <i>HTLV-I</i> : ATLL	<i>n</i> = 12	16.67% (2/12)	West Indies	UK	28–63	<i>Strongyloides</i> : Serology, stool examination <i>HTLV-I</i> : PA [Serodia], WB, EIA	1988–1993	Hoque et al. (1996)	Case studies
<i>Parasites:</i> Strongyloides + HIV <i>HTLV-I</i> : ATLL	<i>HTLV-I</i> = 26 HIV = 98 (10 also had <i>HTLV</i>)	50% (13/26) 10.20% (10/98)	Resident	France	23–95	<i>Strongyloides</i> : Baermann <i>HTLV-I</i> : Unclear	1983–1991	Plumelle and Edouard (1996)	Retrospective case studies
<i>Parasites:</i> Strongyloides	1	1	West Indies	UK		<i>Strongyloides</i> : Duodenal and rectal biopsy <i>HTLV-I</i> : Serology		Shidrawi et al. (1994) and Shidrawi and Westaby (1994)	Case study
<i>Parasites:</i> Strongyloides	1	1	French Caribbean	France	44	<i>Strongyloides</i> : Stool examination (unclear) <i>HTLV-I</i> : Serology	1986–1992	D’Incan et al. (1994)	Case study
<i>Parasites:</i> Strongyloides <i>HTLV-I</i> : ATLL	<i>n</i> = 6	50% (3/6)	Resident	Columbia	17–60	<i>Strongyloides</i> : Stool examination (only if symptoms) <i>HTLV-I</i> : CMIA [Abbott], PA, IF	1988–1991	Blank et al. (1993)	Case studies

Continued

Table 2 Co-infections of HTLV-I and *Strongyloides stercoralis* infection world-wide.—cont'd

Co-morbidity/ HTLV-I disease	HTLV-I prevalence % (p/n)	Parasite prev. % (p/n)	Status or location [#]	Geographical location	Age (years)	Diagnostics	Year	Refs.	Type of study
Parasites: Strongyloides <i>HTLV-I</i> : ATLL	1	1	West Indies	France	35	<i>Strongyloides</i> : Gastroscopy, stool examination <i>HTLV-I</i> : ELISA, PA, WB	1982–1988	Patey et al. (1992)	Case study
Parasites: Strongyloides	1	1	Resident	Senegal	31	<i>Strongyloides</i> : Sputum, stool examination <i>HTLV-I</i> : ELISA, WB	1993	Sane et al. (1994)	Case study
Parasites: Strongyloides	33.72% (29/86) (Ss +) 28.97% (104/359) (Ss –)	13.41% (142/1059)	Resident	Japan	15 to >70	<i>Strongyloides</i> : Agar plate culture <i>HTLV-I</i> : PA		Arakaki et al. (1992a)	Epidemiological
Parasites: Strongyloides	1 6 Ss –	1	West Indies	USA	45	<i>Strongyloides</i> : Bowel biopsy, sputum, serology (IgG, IgE), skin test <i>HTLV-I</i> : ELISA, WB	1897	Newton et al. (1992)	Case study
Parasites: Strongyloides <i>HTLV-I</i> : ATLL	0	1	Guyana	USA	47	<i>Strongyloides</i> : Stool examination, sputum, vomitus <i>HTLV-I</i> : Autopsy	1987	Phelps et al. (1991)	Case study
Parasites: Strongyloides	1	1	Resident	French Guiana	40	<i>Strongyloides</i> : Stool examination <i>HTLV-I</i> : ELISA, WB	1989	Sainte-Foie and Ast-Ravallec (1991)	Case study
Parasites: Strongyloides + Isospora <i>HTLV-I</i> : ATLL	1	1	Japan	USA	52	<i>Strongyloides</i> : Stool examination <i>HTLV-I</i> : EIA	1987	Massey et al. (1990)	Case study
Parasites: Strongyloides	1	1	Resident	Japan	43	<i>Strongyloides</i> : Sputum, stool <i>HTLV-I</i> : Serology (unclear)	1988	Udaka et al. (1990)	Case study

<i>Parasites:</i> Strongyloides	1	1	French West Indies	France	32	<i>Strongyloides</i> : Stool examination, IDA <i>HTLV-I</i> : ELISA, WB	1988	Patey et al. (1990)	Case study
<i>Parasites:</i> Strongyloides	1	1	Resident	Japan	80	<i>Strongyloides</i> : Sputum, stool examination <i>HTLV-I</i> : Serology (IgE)		Furuya et al. (1989)	Case study
<i>Parasites:</i> Strongyloides <i>HTLV-I</i> : ATL	4	4	Japan	USA (Hawaii)	57–71	<i>Strongyloides</i> : Stool microscopy, gastric aspirate, bowel biopsy (postmortem) <i>HTLV-I</i> : ELISA, WB	>1961	Dixon et al. (1989)	Case studies
<i>Parasites:</i> Strongyloides	11.85% (562/4741) [healthy residents] 8.37% (196/2296) [blood donors] 66.12% (203/307) [haematological diseases] 29.24% (422/1443) [other diseases]	23 (11 with HTLV)	Residents	Japan	16–89	<i>Strongyloides</i> : unclear <i>HTLV-I</i> : ELISA, IF, WB	1980–1984	Hanada et al. (1989)	Epidemiological
<i>Parasites:</i> Strongyloides <i>HTLV-I</i> : ATLL	73.63% (67/91) (<i>Ss</i> +) 2.63% (1/38) (<i>Ss</i> –) 61.54% (32/52) (prior <i>Ss</i>)	<i>n</i> = 91	Residents	Japan	33–85	<i>Strongyloides</i> : Stool examination, ELISA (IgG) <i>HTLV-I</i> : PA [Serodia], ELISA	1985–1986	Sato and Shiroma (1989)	Retrospective
<i>Parasites:</i> Strongyloides + Giardia <i>HTLV-I</i> : ATLL	1	1	Dominican Republic	USA	37	<i>Strongyloides</i> : Stool examination <i>HTLV-I</i> : ELISA		Cappell and Chow (1987)	Case study
<i>Parasites:</i> Strongyloides	70.83% (17/24)	<i>n</i> = 27	Resident	Dominica, West Indies	26–91	<i>Strongyloides</i> : Stool examination <i>HTLV-I</i> : ELISA, WB	1995–1999	Adedayo et al. (2002)	Retrospective

Continued

Table 2 Co-infections of HTLV-I and *Strongyloides stercoralis* infection world-wide.—cont'd

Co-morbidity/ HTLV-I disease	HTLV-I prevalence % (p/n)	Parasite prev. % (p/n)	Status or location [#]	Geographical location	Age (years)	Diagnostics	Year	Refs.	Type of study
<i>Parasites:</i> Strongyloides <i>HTLV-I:</i> ATLL	1	1	Africa	France	21	<i>Strongyloides</i> : Previously diagnosed <i>HTLV-I:</i> ELISA, WB	1988–1990	Visy et al. (1993)	Case study
<i>Parasites:</i> Strongyloides	38.89% (14/36)	<i>n</i> = 36	Resident	Japan (Okinawa)	30–91	<i>Strongyloides</i> : Stool examination <i>HTLV-I:</i> IF, pro-viral DNA detection		Nakada et al. (1987)	Targeted cohort
<i>Parasites:</i> Strongyloides	50% (15/30)	53.33% (16/30)	Resident	Japan		<i>Strongyloides</i> : Agar plate culture <i>HTLV-I:</i> PA		Kakazu et al. (1996)	Comparative (H, Ss, HTLV-I –ve & +)
<i>Parasites:</i> Strongyloides	1	1	Resident	Martinique	57	<i>Strongyloides</i> : Stool examination <i>HTLV-I:</i> ELISA, WB	1972–1983	Gessain et al. (1985)	Case study
<i>Parasites:</i> Strongyloides	54.71% (122/223)	11.06% (701/6339)	Resident	Japan	10 to >40	<i>Strongyloides</i> : Agar plate culture <i>HTLV-I:</i> PA	1988–1990	Arakaki et al. (1992b)	Survey
<i>Parasites:</i> Strongyloides	2	2	Resident	Guadeloupe	61, 64	<i>Strongyloides</i> : Stool examination <i>HTLV-I:</i> Serology (unclear)	1992	Foucan et al. (1997)	Case studies
<i>Parasites:</i> Scabies, Strongyloides, <i>Entamoeba</i> <i>histolytica</i> <i>HTLV-I:</i> ATLL	2	1 (Ss) 1 (Scs + Ss)	Resident	Peru	62; 70	<i>Strongyloides</i> : Baermann <i>Strongyloides</i> : Stool examination <i>HTLV-I:</i> EIA		Barros et al. (2012)	Case studies

<i>Parasites:</i> Strongyloides	<i>n</i> = 82	<i>n</i> = 53	Resident	Japan		Previously diagnosed	1984–1985	Barros Kanzaki (2006)	Sero-epidemiological-targeted cohort
<i>Parasites:</i> Scabies, Strongyloides <i>HTLV-I</i> : ATLL	1	1	Morocco	France	24	<i>Strongyloides</i> : Stool examination <i>HTLV-I</i> : Unclear	1994	Dupin et al. (1997)	Case study
<i>Parasites:</i> Strongyloides	1	1	Peru	Italy	35	<i>Strongyloides</i> : Stool microscopy <i>HTLV-I</i> : CMIA [Abbott]	2014	Zammarchi et al. (2015)	Case study
<i>Parasites:</i> Strongyloides Scabies	0.98% (4/409)	0.24% (1/409) <i>Ss</i> 3% (14/409) <i>Ss</i>	Residents	Australia (FNQ)	2–91 years	<i>Strongyloides</i> : Not stated <i>HTLV-I</i> : PA [Serodia], EIA [Murex], CMIA [Abbott]	1999–2016	Smith et al. (2019)	Retrospective review hospital cases
<i>Parasites:</i> Strongyloides	44.9% (22/49)	81.63% (40/49) [27 HTLV-1 + <i>Ss</i>]	Residents	Peru		<i>Strongyloides</i> : Baermann <i>HTLV-I</i> : ELISA, WB	2005–2007	Montes et al. (2009)	Targeted cohort

FNQ, Far North Queensland; QLD, Queensland; WA, Western Australia; NT, Northern Territory; NSW, New South Wales; PA, particle agglutination; WB, Western Blot; EIA, immunoassay; ELISA, enzyme linked immunosorbant assay; PCR, polymerase chain reaction; CMIA, chemiluminescent microparticle immunoassay; *Ss*, *S. stercoralis*; *Ss*, *Sarcoptes scabiei*.

The sensitivity of serological diagnosis for strongyloidiasis varies depending on the test used. Various antigens have been employed, including crude larval extracts of *S. stercoralis* and *S. ratti* and a *S. stercoralis* recombinant antigen (NIE) (Bisoffi et al., 2014). Comparison of three in-house (immunofluorescence antibody test (IFAT), NIE-ELISA, NIE-luciferase immunoprecipitation systems (NIE-LIPS)) and two commercial (Bordier-ELISA, IVD-ELISA) diagnostic assays, using faecal microscopy as the initial standard and a combination of results from all tests as a second standard, showed that the sensitivity of many of the serological procedures was quite low (Bisoffi et al., 2014); and varied between studies (Requena-Mendez et al., 2013). The NIE-ELISA had the lowest sensitivity ranging from 70.77% to 75.44% depending on the standard used, followed by NIE-LIPS (83.85–85.09%), IFAT (93.86–94.62%), with the two commercial kits having sensitivities of 91.23–92.31% for the IVD-ELISA and 89.47–90.77% for the Bordier-ELISA (Bisoffi et al., 2014). Another study reported on the development of an in-house ELISA (AMC-ELISA) and a dipstick assay, which were compared to the commercial IVD-ELISA and Bordier-ELISA. Sensitivity was relatively low in both the IVD and Bordier-ELISAs (89% and 83%, respectively); the best performing test was the AMC-ELISA with a sensitivity of 93%. Specificity was high (>95%) in all tests (van Doorn et al., 2007). In Australia, routine serology is available using the Bordier-ELISA, the IVD-ELISA or the in-house ELISA with similar sensitivity to the two commercial kits.

Serological false negatives can occur in those with acute strongyloidiasis, newly infected individuals who have not yet mounted an immune response, and have been reported in cases of disseminated strongyloidiasis and hyperinfection where immunity is compromised (Marcos et al., 2011; Page and Speare, 2016). Specificity can be affected by cross-reactivity with some other parasite species (Bisoffi et al., 2014; Norsyahida et al., 2013) but as only *Toxocara* and *Fasciola* are endemic in Australia, therefore cross-reactivity is a consideration in the testing of immigrants and returned international travellers but is unlikely to be a problem for those Australians who have not travelled overseas.

2.4 *Strongyloides stercoralis* in Australia

Since 1976 there have been 83 published articles reporting on *S. stercoralis* infection prevalence/incidence in Australia, of which 52 were conducted on residents of Australia; 24 were on refugees, immigrants and returned

travellers; and 7 were on returned services personnel, including former prisoners of war (POWs) and members of peace-keeping forces (Table 1). There was some overlap in some of the reports on infections in residents, immigrants and Australian Defence Force (ADF) personnel in the same paper. Of the 64 papers published on *S. stercoralis* infection, 17 indicated co-infection with HTLV-I (Table 1). The majority of articles (totalling 45) citing data on Australian residents involved Indigenous Australians, while some studies did not specify the target group (Table 1).



3. HTLV-I background

HTLV-I was the first retrovirus to be identified and was isolated in the late 1970s (Gallo, 2005). However, two manifestations of HTLV-I had been observed prior to its isolation; a myelopathy known as tropical spastic paraparesis (TSP) and a leukaemia known as Adult T-cell leukaemia/lymphoma (ATLL) or cutaneous T-cell lymphoma (Satoh et al., 1991). Two types of HTLV exist and are known as HTLV-I and HTLV-II. A third type, HTLV-III, often referred to in earlier articles as the causative agent of AIDS, is now recognized as the human immunodeficiency virus (HIV) (Abe, 1986; Bayley et al., 1985). HTLV-II is considered less pathogenic than HTLV-I and is rarely associated with human disease; it has been associated with myelopathy but not with leukaemia (Dooneief et al., 1996; Harrington Jr. et al., 1993; Hjelle et al., 1992; Jacobson et al., 1993; Murphy et al., 1997; Sheremata et al., 1993).

3.1 Disease caused by HTLV-I

The majority (>90%) of HTLV-I-infected persons are asymptomatic carriers, although there are some immunological differences in these carriers compared with healthy controls (see Section 5) (Robinson et al., 1994; Satoh et al., 1991). HTLV-I can increase susceptibility to other pathogens, including respiratory and urinary tract infections, and cause sexual complications such as erectile disruption (de Oliveira et al., 2017; Oliveira et al., 2007; Rocha et al., 2007). It also increases the severity of strongyloidiasis and can lead to dissemination and hyperinfection as there are increased levels of pro-inflammatory cytokines and decreased levels of anti-inflammatory cytokines in individuals infected with HTLV-I (Banerjee et al., 2007; Futsch et al., 2018). It is noteworthy that strongyloidiasis itself may also increase the severity of HTLV-I-induced disease as *S. stercoralis* infection results in reduced levels of pro-inflammatory cytokines and increased levels

of anti-inflammatory cytokines (Anuradha et al., 2015; Robinson et al., 1994; Satoh et al., 1991).

There are two main disease states recognized in HTLV-I-infected individuals that seroconvert and exhibit clinical symptoms—adult T-cell leukaemia/lymphoma (ATLL) and HTLV-I associated myelopathy/tropical spastic paraparesis (HAM/TSP). ATLL, which has acute, chronic, lymphomatous, and smouldering forms, is the most common disease state associated with HTLV-I. ATLL is a haematological malignancy that predominantly affects CD4⁺ T-cells, although pro-viral DNA is also detectable but to a lesser extent in CD8⁺ T-cells, B cells, dendritic cells, and monocytes (Gross and Thoma-Kress, 2016; Koyanagi et al., 1993). The acute form occurs in ~50% of ATLL cases and is characterized by fever, lymphadenopathy and opportunistic infections. The average life-expectancy of an individual with acute ATLL is 6 months (Alves and Dourado, 2010). Chronic ATLL occurs in ~20% of cases and can remain dormant for years before suddenly transforming into the acute form. A further 20% of those infected develop the lymphomatous form which primarily occurs in solid lymphoid tissue, and ~5% develop the smouldering subtype which is characterized by abnormal lymphocytes in the peripheral blood. Symptoms of ATLL include fatigue, rash, enlarged lymph nodes and hypercalcaemia, which can lead to confusion, bone pain and severe constipation (Alves and Dourado, 2010).

HAM/TSP affects the central nervous system and, prior to the link to HTLV-I being established, was known solely as tropical spastic paraparesis (TSP). It is characterized by demyelination of grey and white matter, and increasing atrophy of the spinal cord presenting as back pain, progressive weakness, stiffness and leg pain, and mild cognitive impairment (Taniguchi et al., 2017). Urinary disturbance or incontinence is also observed with HAM/TSP (Matsuura et al., 2016). HAM/TSP can progress rapidly (<2 years) or quite slowly (>15 years) and significantly impacts on an infected patients' ability to walk (Matsuura et al., 2016).

HTLV-I-associated disease in children may present atypically, although both ATLL and HAM/TSP have been reported. More common in children infected with HTLV-I is infective dermatitis (ID) which is often recurrent, but can also occur in adults; skin manifestations are also common in ATLL (Clyti et al., 2004; Gabet et al., 2003; Menz et al., 2018) (Table 2). ID in children may be associated with the early development of ATLL (Oliveira et al., 2018) and is characterized by severe recurrent eczematous skin change, distinguishable from infant eczema. As well as an early indicator of HTLV-I infection, ID can also be a sign of leukaemia (Trope and Lenzi, 2009).

Due to the immunosuppressive aspects of HTLV-I, patients are at risk of opportunistic infection with a range of bacterial, viral, and parasitic infections, even if their HTLV-I status is considered asymptomatic (Tanaka et al., 2015). For example, cytomegalovirus (CMV) gastritis, *Pneumocystis*, strongyloidiasis hyperinfection, pulmonary histoplasmosis, cryptococcal meningitis, and disseminated herpes zoster are more severe in HTLV-I-infected individuals (Agut et al., 1988; Bonin et al., 2010; Boulos et al., 1992; Chang et al., 1998; Einsiedel et al., 2014a, b; Figueiro-Filho et al., 2007; Foucan et al., 1997; Fujii et al., 1993; Gallo, 1988; Guo et al., 2015; Higashiyama et al., 1997; Honarbakhsh and Taylor, 2015; Mukerjee et al., 2003; Riedel et al., 2008; Satoh et al., 2003; Sugiura et al., 2006; Tanaka et al., 2015; Troncoso Garcia et al., 2000; Wang et al., 2014). Bacterial meningitis is a particularly common occurrence in case studies of HTLV-I (Foucan et al., 1997; Funakawa et al., 1993; Furuya et al., 1989; Higashiyama et al., 1997; Hovette et al., 2002; Kawano and Kira, 1995; Phelps et al., 1991; Riedel et al., 2008; Saito et al., 1988; Sasaki et al., 2013; Satoh et al., 2003; Schein et al., 2018; Sugiura et al., 2006; Tanaka et al., 2015; Troncoso Garcia et al., 2000; Yokota et al., 1988; Zammarchi et al., 2015).

In community-wide studies in Japan the majority of individuals infected with HTLV-I were older than 50 years, possibly indicating an increase in the cumulative risk of infection over time (Hirata et al., 2006; Nakada and Knight, 1984). It may also be representative of the fact that while the majority of people become infected as infants via breastmilk, it can take decades before the disease state develops (Matsuura et al., 2016). Additionally due to interventions against breast feeding among HTLV-I-positive mothers there has likely been an overall decrease in the occurrence of new infections there.

3.2 Transmission

HTLV-I predominantly exists in a pro-viral state. As a single-stranded RNA (ssRNA) virus, HTLV-I is converted to double-stranded DNA (dsDNA) and inserts itself into the cell nuclear DNA (Grassi et al., 2011; Verdonck et al., 2007). HTLV-I viral load in blood is comparatively low compared with the closely related HIV virus. Unlike HIV, which utilizes this high circulating viral load to infect T-cells, HTLV-I infects T-cells using a 'viral synapse', facilitating direct cell-to-cell infection and by mitotic division of cells. The pro-viral load determines HTLV-I infection outcomes. In 'asymptomatic' HTLV-I-infected individuals the pro-viral loads remain stable while those who go on to develop symptomatic infections have higher

pro-viral loads (Einsiedel et al., 2016a; Grassi et al., 2011; Primo et al., 2009). Higher HTLV-I pro-viral loads are associated with bronchiectasis and blood stream infections in Australian Aboriginals (Einsiedel et al., 2016a). Co-infection with *S. stercoralis* has also been associated with higher pro-viral loads (Gillet et al., 2013). There was an increase in the clonal population of HTLV-I-infected cells in those infected with *S. stercoralis* compared with those who were uninfected but asymptomatic for HTLV-I; however, the highest pro-viral loads were evident in those manifesting ATLL without *S. stercoralis* infection (Gillet et al., 2013). There is no retroviral treatment for HTLV-I or HTLV-II (Futsch et al., 2017; Pasquier et al., 2018).

Transmission of HTLV-I occurs via breast feeding, transfusions with cellular blood products, or through sexual contact. The rate of infection via sexual contact varies from male to female, with females much more likely (40%) to be infected by male partners than the other way around (Bandeira et al., 2018; Kajiyama et al., 1986). In Japan, pregnant women in hyper-endemic areas are screened to prevent HTLV-I transmission to children via breast milk (Hino et al., 1985, 1986, 1987a, b; Sugiyama et al., 1986).

The primary source of HTLV-I virus in breast milk is infected T-cells present in the breast milk, rather than cell-free viral particles which have not been detected (Li et al., 2004). HTLV-I-infected lymphocytes are a strong candidate for breast milk transmission with breast-fed children ingesting an estimated 10^8 lymphocytes per day (Kinoshita et al., 1984, 1987; Percher et al., 2016). Other cells that can be infected and are also found in breast milk are macrophages and skin epithelial cells (Percher et al., 2016).

HTLV-I infection occurs in temperate as well as in tropical and subtropical zones. As it is transmitted person-to-person there are no environmental factors, such as high temperature, preventing transmission.

3.3 Diagnosis

HTLV-I infection is primarily diagnosed by antibody detection in blood or cerebrospinal fluid, although polymerase chain reaction (PCR) diagnosis is also used (Thorstensson et al., 2002); diagnosis of ATL and HAM/TSP is usually made based on observed symptoms (NORD, 2019). There are several commercially ELISA-based test kits available for HTLV-I diagnosis (Abbott, 2019; annardx, 2019; Fujirebio, 2019). Western blotting (WB) is primarily used as a confirmatory test after a positive result by ELISA or other serological test (Tables 1 and 2).

There is no commercially available diagnostic PCR for HTLV-I, but there are several in-house assays that have been used in conjunction with the immunoassays. Quantitative real-time PCR (qPCR) is particularly useful for determining the pro-viral load of HTLV-I in infected individuals, which may be important for determining the change from an asymptomatic infection to symptomatic disease (i.e., ATLL or HAM/TSP) (Gabet et al., 2000). Digital droplet PCR (ddPCR), a fully quantitative method, has also been used for determining pro-viral loads (Hedberg et al., 2015; Thulin Hedberg et al., 2018).

A comparison of a specific PCR with commercially available immuno-diagnostics (ELISA, WB) found that all techniques had high sensitivity for detecting HTLV-I infection, although PCR and WB had low sensitivity for HTLV-II (Thorstensson et al., 2002). A more recent study compared the performance of four commercially available kits, with WB used as the initial screening measure and gold standard, with PCR confirmation for WB-indeterminate samples (da Silva Brito and Santos, 2018). The kits tested were three ELISA assays, and one chemiluminescence microparticle immunoassay (CMIA) (da Silva Brito and Santos, 2018). All tests exhibited 100% sensitivity while specificity varied. Specificity was highest for SYM and Gold ELISA (REM, 2020) (>99.5%), followed by Abbott/Architect (98.1%), and then Murex (92%) (da Silva Brito and Santos, 2018).

3.4 HTLV-I in Australia

Autochthonous cases of HTLV-I in Australia have primarily been reported in remote Aboriginal communities in Central Queensland (CQ), Far North Queensland (FNQ) the Northern Territory (NT), and Northern Western Australia (WA) (Table 1, Figs. 2 and 3). In FNQ, serological testing for HTLV-I increased markedly from 1999 (<5 tests) to 2016 (>120 tests), with the most significant increase occurring between 2015 (<40 tests) and 2016 (Smith et al., 2019), indicating an increased awareness of HTLV-I in FNQ. A total of 27 papers describing HTLV-I infection or case studies were reported from Australia; of these 17 reported co-infections with *S. stercoralis* (Table 1). In the last 10 years (2010–2019) there have been 20 studies reporting on strongyloidiasis or HTLV-I in Australia; only two identified co-infections and five identified HTVL-I only (Table 1).

The Australian Red Cross began testing all cellular products for HTLV-I in 1992 (Whyte, 1993, 1997), and has only recently switched from testing every blood donation for HTLV-I to only testing new blood



Fig. 2 Geographical locations of identified *Strongyloides stercoralis* and HTLV-I cases and prevalence studies undertaken in Australia (1976–2019), based on data from [Table 1](#).

donors ([Styles et al., 2018](#)). In the 2004–2014 period the prevalence of HTLV-I among blood donors was 3 in every million donations; HTLV-I testing costs \$3 million annually ([Styles et al., 2017](#)). Internal data of the Red Cross estimated HTLV-I prevalence to be 1 in 75 million blood donations, and new donor testing was considerably less expensive at \$225,000 annually than testing all blood donations ([Styles et al., 2017](#)). Focal areas of HTLV-I transmission in remote communities in Australia are often >1000 km away from a blood donation centre, reducing the likelihood of blood donations from endemic areas ([Styles et al., 2017](#)) ([Fig. 2](#)). The infection rate of HTLV-I in blood donation recipients has been previously calculated as 27%, and, more recently, at 60% seroconversion via blood transfusions ([Ikeda et al., 1998](#); [Whyte, 1997](#)); therefore not

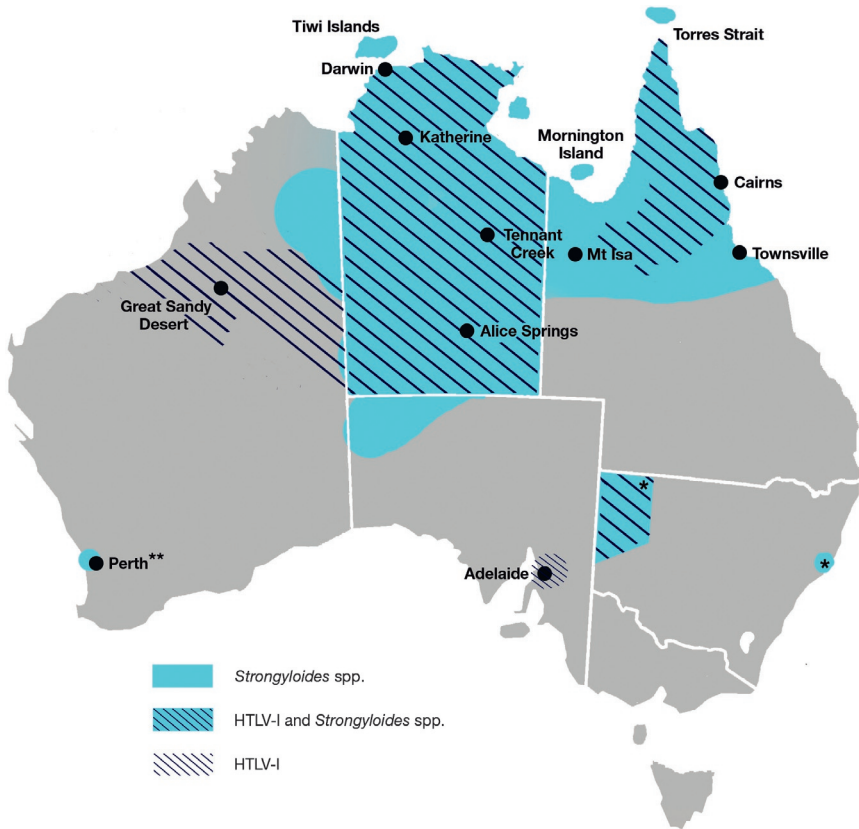


Fig. 3 HTLV-I and *Strongyloides stercoralis* infections published in Australia from 2010 to 2019.

everyone treated with HTLV-I-contaminated blood products would be infected, but some risk remains (Whyte, 1997). While the prevalence of HTLV-I in Australian blood donors is low, targeted testing of donors at risk of contracting HTLV-I infection each time they donate may be beneficial to further safeguard the Australian blood supply given HTLV-I infection can have the very severe consequences described, including death.

In May 2018 the Australian Federal Government pledged 8 million dollars (AUD) for research on communicable diseases in Aboriginal populations with a focus on HTLV-I (Australian Government Department of Health, 2018). The communique from the Collaborative Human T-Lymphotropic Virus Type-1 Forum held in August 2018 reaffirmed the ‘importance of Aboriginal leadership in this process’ (HTLV-Aware, 2018).



4. HTLV-I co-infections with *Strongyloides stercoralis*

As indicated earlier, HTLV-I and *S. stercoralis* infections in Australia occur in three main cohort groups. The first comprises refugees and immigrants (Chan et al., 2018; Chaves et al., 2009; de Silva et al., 2002; Einsiedel and Spelman, 2006; Ford et al., 1981; Grant and Tiong, 2018; Gurry et al., 2015; Lim and Biggs, 2001; Mukerjee et al., 2003; Ngo et al., 2018; Paxton et al., 2012; Prociv and Adkins, 1987; Rice et al., 2003; Sampson and Grove, 1987; Zubrinich et al., 2019); the second is Aboriginal Australians in remote areas who acquire HTLV-I and *S. stercoralis* locally (Einsiedel et al., 2013, 2014b, 2016a, c, 2018; Einsiedel and Fernandes, 2008; Einsiedel and Woodman, 2010; Smith et al., 2019); and the third are returned service personnel who served overseas (Grove, 1980; Heath et al., 1996; Kennedy et al., 1989; Mukerjee et al., 2003; Oliver et al., 1989; Pattison and Speare, 2008; Rahmanian et al., 2015; Yiannakou et al., 1990) (Table 1). Returned travellers who have travelled to endemic areas and become infected make a fourth, smaller infection cohort (Einsiedel and Spelman, 2006; Heath et al., 1996) (Table 1).

There are several subtypes of HTLV-I, with subtype c the primary viral subtype in Australia, Papua New Guinea, the Solomon Islands and Vanuatu (Cassar et al., 2013; Verdonck et al., 2007). Phylogenetic analysis of HTLV-I from individuals presenting to Alice Springs hospital in Central Australia identified at least two clades of subtype c present in Australia (Cassar et al., 2013). The analysis was based on sequencing the LTR, *gag*, and *tax* regions of HTLV-I of 19 individuals, and whole genome sequencing for 4 individuals. These were compared to other available HTLV-I sequences, and four sequences from Vanuatu were also examined in this study. The Australian sequences were distinct from the Vanuatu and Papua New Guinea/Solomon Island clades (Cassar et al., 2013). HTLV-I in Australia originated from ancient human migration. The development of the two Australian clades is likely due to continued evolution of the virus in isolated groups of Indigenous Australians in remote regions of Central Australia. HTLV-I in Australia is associated with respiratory disease including bronchiectasis; although the causal relationship is not definitive, those who develop bronchiectasis have very high viral loads of HTLV-I (Einsiedel et al., 2012, 2014b, 2016a, 2018; Honarbakhsh and Taylor, 2015).

Estimating the true infection prevalence of *S. stercoralis* in Australia is challenging due to differences in diagnostic recording in hospitals, and a lack

of community-wide prevalence-based studies. Scrutiny of the literature revealed only one paper reporting on both HTLV-I and *Strongyloides* in Central Australia that fits the requirement of a community survey; 40% (30/74) of those tested were positive for HTLV-I and 14% (10/72) were positive for *S. stercoralis* (Einsiedel et al., 2016c). All other studies published to date showing infection with HTLV-I and *S. stercoralis* are based on retrospective targeted hospital-based cohorts or case studies (Table 1). Since 1976, 64 articles recorded *S. stercoralis* infections in Australia; 17 papers also diagnosed co-infection with HTLV-I; and 11 reported HTLV-I infection alone (Table 1). There is a lack of diagnostic testing of *S. stercoralis* in cases where HTLV-I is identified and vice versa; as remote communities in the North of Australia are endemic for both pathogens it is important to diagnose individuals harbouring co-infections. As previously mentioned, co-infection with HTLV-I can cause hyperinfection and dissemination of *S. stercoralis* which can result in death if not appropriately treated. A retrospective study (2000–2006) from Alice Springs hospital in central Australia identified 18 cases of probable complicated strongyloidiasis, 9 were determined as definite strongyloidiasis and 9 as probable strongyloidiasis; 11 cases were tested for HTLV-I with seven proving positive (Einsiedel and Fernandes, 2008). Of the definite strongyloidiasis cases, three were never treated for strongyloidiasis and two cases were initially treated with albendazole, which is not the most effective treatment for strongyloidiasis. This pattern was also evident in the probable strongyloidiasis cases with no treatment for strongyloidiasis in five of these subjects (Einsiedel and Fernandes, 2008). Mortality due to strongyloidiasis can be high in immunosuppressed persons, such as those who are co-infected with HTLV-I. Correct diagnosis of concurrent HTLV-I and strongyloidiasis is absolutely essential for correct case management. In the retrospective study by Einsiedel and Fernandes (2008) 15 of the 18 cases resulted in death which may have been avoided by early diagnosis and correct treatment for strongyloidiasis. Death was caused in most cases by bacterial sepsis, a known complication of disseminated strongyloidiasis (Fig. 1).

From scrutiny of Table 2 it appears there is no preponderance of *Strongyloides* infection in HTLV-I-positive individuals but there may be an argument for a relationship between HTLV-I seroconversion and high intensity *Strongyloides* infections, and increased likelihood for disseminated strongyloidiasis in HTLV-I-infected persons (Robinson et al., 1994; Satoh et al., 1991). If HTLV-I increases susceptibility to infection with *Strongyloides* then higher prevalence should be evident in HTLV-I-infected individuals compared with those uninfected with HTLV-I. Polyparasitism

with individuals infected concurrently with both helminth and protozoan parasites are common in endemic areas (Gordon et al., 2015; Weerakoon et al., 2018); it is, therefore, highly likely that a virus such as HTLV-I that occupies the same ecological niche will also co-infect an individual harbouring a helminth parasite such as *S. stercoralis*.

The true burden of co-infection of HTLV-I and *S. stercoralis* in Australia is, therefore, unknown but as a recent review emphasized in relation to strongyloidiasis that could also be applied to HTLV-I: ‘chronic strongyloidiasis—don’t look and you won’t find’ (Page and Speare, 2016).

4.1 Prevalence

The majority of reports identified in this review were case studies, with the few larger hospital cohort studies based on testing blood donors, retrospective examinations of past patients in a hospital setting, and targeted cohorts known to have either an HTLV-I or *Strongyloides* infection. Five papers that considered both HTLV-I and *S. stercoralis* infections met the criteria for a community-wide survey or cross-sectional study that specifically sampled communities or villages in endemic areas, with four from Japan (in English) (Arakaki et al., 1992a, b; Hayashi et al., 1997; Higashiarakawa et al., 2017), but only one from Australia (Einsiedel et al., 2016c) (Table 2). In the Australian cohort study, 97 of 138 members of a single remote Aboriginal Community in Central Australia had their HTLV-I status determined and, of these, 72 subjects were tested for strongyloidiasis (Einsiedel et al., 2016c). Only one child (<14 years of age) was infected with HTLV-I; adults were significantly more likely to be infected with 40.5% ($n=74$) adults being seropositive for HTLV-I. *Strongyloides* infection was not associated with HTLV-I infection, although overall sero-prevalence was low in this community with only 10 cases identified, 6 in HTLV-I-positive individuals, and 4 in HTLV-I negative individuals (Einsiedel et al., 2016c). In addition to strongyloidiasis, scabies was also detected in one child who had discordant results for HTLV-I but whose family were HTLV-I-positive (Einsiedel et al., 2016c).

A survey of hospital data from Queensland (1998–2002) found 120 cases where a positive laboratory diagnosis of strongyloidiasis was made (Hutchinson, 2003; Shield and Page, 2008). Lack of accurate diagnostic tests has also resulted in confusion, with one study classifying subjects with strongyloidiasis symptoms later reporting that some of the uninfected control patients were also infected with *Strongyloides* (Grove, 1989; Shield and Page, 2008).

Considering the four Japanese cohort studies, there were no significant differences in *Strongyloides* prevalence between the HTLV-I-positive and HTLV-I-negative individuals (Table 2) (Arakaki et al., 1992a, b; Hayashi et al., 1997; Higashiarakawa et al., 2017). It is notable that the prevalence of both HTLV-I and *Strongyloides* has decreased significantly in Japan; over the past 70 years this decrease in prevalence is likely due to increased socio-economic development and improved sanitation (Tanaka et al., 2016). Testing of pregnant Japanese women for HTLV-I and the switch to bottle feeding in HTLV-I-positive mothers have proved effective in reducing transmammary transmission of the virus, at a rate estimated to be about 20–30% (Ando et al., 1987, 1989, 2003; Ikeda et al., 1998; Kinoshita et al., 1987).

4.1.1 Refugees and immigrants in Australia

In the 2017–2018 period, 526,300 immigrants and refugees came to Australia (ABS, 2019). While this number was down on previous years, the majority of new arrivals came from countries in Asia (China, India, the Philippines, Vietnam, Malaysia, Sri Lanka, South Korea, Hong Kong, and Indonesia) and Oceania (ABS, 2019). Just over 7 million people recorded a country of birth other than Australia (29.4% of the total population) in 2018. The highest immigrant group by birth came from England (4.0%) followed by China (2.6%), India (2.4%), New Zealand (2.3%), the Philippines (1.1%), Vietnam (1.0%), South Africa (0.8%), Italy (0.7%), Malaysia (0.7%), and Scotland (0.5%) (ABS, 2019).

Asia is highly endemic for STH, including *S. stercoralis* (Jex et al., 2011; Khieu et al., 2013), and a range of other infectious diseases including HTLV-I (Gessain and Cassar, 2012). Of countries on the immigrant list with the largest populations by birth outside of Asia, Lebanon and South Africa are also endemic for STH, *S. stercoralis* and HTLV-I. There are therefore a considerable number of individuals entering Australia that may have been exposed to and harbour a number of infectious diseases (ABS, 2019). Immigrants and refugees diagnosed in Australia since 1976 with *S. stercoralis* originated from a range of countries, including Laos, China, Cambodia, India, Sri Lanka, Myanmar, Vietnam, Japan, Sierra Leone, and Sudan, all of which are endemic for both *S. stercoralis* and HTLV-I (Tables 1 and 2) (Biggs et al., 2009; Bradbury and Thomas, 2006; Caruana et al., 2006; Chan et al., 2018; de Silva et al., 2002; Grant and Tiong, 2018; Gurry et al., 2015; Mukerjee et al., 2003; Ngo et al., 2018; Paxton et al., 2012;

Prociv and Adkins, 1987; Rice et al., 2003; Sampson and Grove, 1987; Yong et al., 2007).

The majority of studies identifying *S. stercoralis* infection in immigrants and refugees in Australia, used either serology, faecal examination by various methods, or a combination of both as diagnostic tools (Tables 1 and 2). International guidelines and the Australian Therapeutic Guidelines recommend screening patients at epidemiological risk of *S. stercoralis* prior to the initiation of immunosuppressive therapy. Chemoprophylaxis is also recommended for patients shown to be serologically-positive for *Strongyloides*, and patients who are negative by serology but who have lived in or visited an area endemic for *S. stercoralis* (CDC, 1993; Requena-Mendez et al., 2013). International guidelines also require serology and faecal examination prior to immunosuppression or for those already immunosuppressed (Requena-Mendez et al., 2013).

One of the most extensive *S. stercoralis* studies performed in Australia was that on refugees from Myanmar (2006–2008) (Paxton et al., 2012). Of 973 individuals tested for *S. stercoralis*, 20.8% (202/973) were positive, while 43.4% (446/1027) were positive for ‘faecal pathogens’ by faecal microscopy which may also have captured some *S. stercoralis*-positive subjects. A more recent study (2013–2014) on refugees from various countries identified a smaller prevalence of *S. stercoralis* by serology—4.1% (136/3307) subjects were positive with 2.2% (73/3307) being equivocal (Ngo et al., 2018). The lower prevalence is likely due to the inclusion of all refugees in the survey, some of which originated from non-endemic or low *S. stercoralis* transmission areas.

Other recent papers on immigrants or refugees in Australia include two case studies of immigrants from Vietnam (Chan et al., 2018; Grant and Tiong, 2018), and another reporting on four case studies of immigrants from Vietnam, India, Fiji, and Japan (Zubrinich et al., 2019). A cohort study on Cambodian refugees in 2002 determined a *S. stercoralis* prevalence of 36% ($n=234$) (Biggs et al., 2009). Those positive had all been resident in Australia between 2 and 28 years. The patients were diagnosed by serology or faecal testing and treated with ivermectin. Of the 82 positives, 40 were followed up after treatment, with 21 still giving positive serology at 3 months posttreatment. However, an overall decrease in antibody levels was detected. In another hospital data survey, 20% of faecal samples from 2686 refugees, many being new arrivals from Sierra Leone, Sudan, Ethiopia, Uganda and Somalia, tested at the Royal Hobart Hospital between 2002 and 2005, were shown to be *S. stercoralis*-positive (Bradbury and Thomas, 2006).

S. stercoralis can be a very persistent parasite, as evidenced by immigrants returning positive results years after settlement in Australia (Biggs et al., 2009; Einsiedel and Spelman, 2006); and returned service personnel, particularly Vietnam veterans (Rahmanian et al., 2015) and WWII ex-POWs imprisoned in Thailand (Grove, 1980; Oliver et al., 1989), who were found to be positive for *S. stercoralis* many years after they had left an endemic area.

Whereas we found no specific publications relating to the HTLV-I status in refugees and immigrants arriving in Australia, studies on refugees arriving in the USA from South East Asia revealed zero to very low (0.6%; $n=193$) HTLV-I prevalence (Belongia et al., 1991; Buchwald et al., 1992); prevalence was higher in African refugees, with an HTLV-I prevalence of 2.3–5.4% ($n=398$)=in Mozambiquans from two refugee camps in Swaziland (Van Rensburg et al., 1995). A separate study on African refugees from Zaire, Ghana, and South Africa in Belgium reported a HTLV-I prevalence of 4% ($n=4, 603$) (Goubau et al., 1993).

4.1.2 Returned service personnel

While there are data on *Strongyloides*, no information is available for concurrent *Strongyloides* and HTLV-I infections in returned service personnel, and there is also limited information on potential HTLV-I infections in this group. Australia's armed services have been involved in wars, occupations, and peace-keeping missions around the world, many in areas endemic for *S. stercoralis*, HTLV-I, and other infectious diseases. Countries in which the armed services have been employed since the second world war include Korea, Papua New Guinea, Timor Leste, Japan, Malaysia, Zimbabwe, Rwanda, Vietnam, Iraq, Afghanistan, Cambodia, India and Pakistan, as well as postings in Island nations around the Pacific Ocean, all of which are endemic for *S. stercoralis*. Due to the ability of *S. stercoralis* to autoinfect, it can be very persistent and long-lived in humans (Montes et al., 2010). Six papers reported on the diagnosis of *S. stercoralis* in ADF or peacekeeping forces personnel (Table 1), but no HTLV-I infections were recorded in these two groups. Nevertheless, a statement of principles concerning HTLV-I and the Veterans Entitlements Act of 1986, tabled in 1996 (Australian Government, 1996), indicated that it was recognized as a public health issue although it is unclear if the Australian army ever conducted HTLV-I testing on returned service personnel. It seems unlikely that such a statement would have been released if there was no possibility of HTLV-I infection in returned service personnel.

In 2013 a pilot study, examining the prevalence of *S. stercoralis* in Australian veterans of the Vietnam War (Australian involvement 1962–1975), was undertaken (Rahmanian et al., 2015). Of the 249 veterans enrolled in the study, 11.6% proved seropositive for *S. stercoralis* using a commercially available ELISA. Three consecutive stool samples were then taken from all seropositive individuals and subjected to microscopy after the samples were concentrated to identify larvae. None of the samples from the seropositive individuals were positive by microscopy, but as the authors stated they used direct smear and formol–ether concentrates, which are comparatively insensitive diagnostic methods. There was a significant increase in dermatological symptoms in the seropositive individuals compared with those who were seronegative, although not with gastrointestinal indicators, and eosinophilia was not associated with seropositivity (Rahmanian et al., 2015).

In an earlier case study (Kennedy et al., 1989), a patient, who was a former POW held in Thailand in 1943–44 during WWII, was initially treated for lung cancer at the age of 65; after subsequent identification of necrosis in the bowel, the necrotic section was removed and larvae of *S. stercoralis* were identified in the removed section. Both larvae and ova were subsequently identified in the POW's sputum during the 6 days post diagnosis of *S. stercoralis* and the commencement of treatment with thiabendazole. During his cancer treatment he had not been treated with immunosuppressive drugs, and it may have been his age-related immunosenescence and the effect the cancer was having on his immune system pre-diagnosis which may have caused hyperinfection, in this case, more than 40 years after being held as a POW. A more extensive study conducted in 1980 on POWs (1942–1945) held in South East Asia (SEA) identified *S. stercoralis* in 44 (27.5%) of 160 individuals enrolled in the study (Grove, 1980). All participants were members of the same battalion that were captured in Singapore and then were sent to various POW camps in SEA and Japan, including working on the Burma–Thailand railway (Grove, 1980). A similar study (1989) in Tasmania determined a *S. stercoralis* prevalence of 17% ($n=150$) in POWs (1942–1945) held in various locations around SEA (Timor, Java, Singapore, Burma–Thailand, Japan) (Oliver et al., 1989). More recently (2003), 14 *S. stercoralis* cases were identified in the Regional Assistance Mission to Solomon Islands (RAMSI) personnel (Pattison and Speare, 2008).

The majority of studies investigating the presence of *S. stercoralis* in veterans and service personnel were undertaken decades after they returned

from endemic areas where they would have been infected. Closer monitoring of returned service personnel in the years directly following their deployment and follow up in those who test positive to *S. stercoralis* would be beneficial for the long-term health of veterans.

4.1.3 Australian aborigines in remote communities

Indigenous Australians in remote communities have high prevalence of strongyloidiasis with estimates ranging from 10% to 60% depending on the community tested and the diagnostic tools used (Flannery and White, 1993; Kearns et al., 2017; Prociw and Luke, 1993; Sampson et al., 2003; Shield et al., 2015). Strongyloidiasis is associated with socioeconomic disadvantage (Beknazarova et al., 2016) and the endemic nature of the disease in remote communities supports this. As early as 1990 it was suggested that with appropriate disposal of human faeces strongyloidiasis is rarely seen (Grove, 1990); however, safe water and effective sanitation alone do not lead to elimination of strongyloidiasis (Shield and Page, 2008). Furthermore, levels of infection are likely to be underestimated as many clinical staff are unaware of the disease (Page and Speare, 2016), and deaths can be recorded as sepsis rather than due to strongyloidiasis (Einsiedel and Fernandes, 2008). The majority of *S. stercoralis* infections in Australian residents identified in this review were in Aboriginal Australians (Table 1).

The latest Australian census in 2016 indicated the highest number of Aboriginal and Torres Strait Islanders (ATSI) is resident in New South Wales (NSW) (254,842) followed by Queensland (QLD) (176, 910) and then Western Australia (WA) (96,497) (ABS, 2018a). Over one-third (37.4%) of ATSI live in major cities while 6.7% and 11.9% live in remote and very remote areas, respectively. Many of these remote and very remote areas are in the Northern Territory (NT) and WA (ABS, 2018a; Biddle and Markham, 2016). The majority of studies written about strongyloidiasis in Australia, and identified in our literature searches, were performed in the NT, specifically in Alice Springs and Darwin (Table 1). These are the two main centres in the NT with major hospitals. Many of the surrounding communities can be hundreds to thousands of kilometres (km) away from these centres, which impacts on the health services provided for individuals living in remote/very remote areas. Alice Springs Hospital (ASH) services an area of 1,000,000 km² and a population of 47,000 of which, 40% are Aboriginal and Torres Strait Islanders (ATSI) who make up 70% of patients at ASH (Einsiedel et al., 2012). Darwin has a

population of 148,564, of which 8.7% identify as ATSI, and services an area of 3163.9 km² (ABS, 2018b).

We identified a total of 68 papers that considered HTLV-I and *S. stercoralis* infection in Australian residents, although concurrent infections were only identified in 12 articles (Table 1). The largest of these studies were in Alice Springs with two reports of parasitological data for 1847 individuals and HTLV-I data for 2454 individuals; 180 individuals had concurrent HTLV-I and *S. stercoralis* infections (Einsiedel et al., 2014b, 2018). Elsewhere, only one co-infection was identified in FNQ and three from Perth, WA (Boan et al., 2017; Robertson et al., 2017; Smith et al., 2019) (Table 1, Figs. 2 and 3).

The retrospective (2000–2006) Alice Springs case study on co-infections of HTLV-I and *S. stercoralis* referred to earlier, identified a lack of effective treatment of *S. stercoralis* after a positive diagnosis—either via stool or serology (Einsiedel and Fernandes, 2008).

The lack of adequate treatment of strongyloidiasis in ASH may be due to a lack of appropriate recognition of the seriousness of *S. stercoralis* infection in the immunosuppressed, such as can occur in co-infections with HTLV-I, and, as one group of authors put it, an ‘inability to maintain core knowledge’ (Einsiedel et al., 2018). In remote areas of Australia, health staff turnover can be quite rapid, leading to loss of knowledge as no appropriate database has been established to retain this information. This has, in part, resulted in a call to have human strongyloidiasis designated as a notifiable disease in Australia, which would allow for greater visibility of the disease, and provide guidance for effective treatment (Beknazarova et al., 2018).

A study conducted in 2010–2011 in the Top End (NT) determined a prevalence of 21% ($n=818$) for *S. stercoralis* by serology and/or faecal culture (Holt et al., 2017a; Kearns et al., 2017). Treatment consisting of one dose of ivermectin (200 µg/kg), or daily doses of albendazole for 3 days for children weighing <15 kg, was given at the time of sample collection to all non-pregnant subjects and repeated if they tested positive for *Strongyloides*. After treatment the prevalence was reduced drastically to 5% at month 6, and to 2% after a second dose of ivermectin given to those still positive at month 12, showing that correct and appropriate treatment greatly impacts infection levels in endemic areas. In initially negative individuals, when retested after 12 months, 2.5% (4/157) were positive for *Strongyloides*, giving a measure of the infection rate. A subsample of dried blood spots collected as finger pricks on filter paper from children who did not provide venous blood samples determined a *S. stercoralis* sero-prevalence of 16.5%

($n=124$) prior to treatment, but a much less marked decrease in prevalence (12%) was observed 6 months after treatment ($n=30$) (Mounsey et al., 2014). It should be emphasized that children weighing less than 15 kg were given albendazole for 3 days instead of ivermectin in this study which may impact on cure rates as ivermectin is the recommended drug for strongyloidiasis.

Another investigation, primarily examining diabetes in Australian Aborigines, was conducted in Western Australia (WA) and reported a *S. stercoralis* prevalence of 35.5% ($n=259$) at baseline (undertaken in 2012), with serological cure (after ivermectin treatment) of individuals was characterized by ELISA-negativity; 5.8% were positive after 3 years (Hays et al., 2017a, b). A more recent analysis of faecal microscopy results from 2008 to 2018 in the NT determined a 0.48% ($n=49,679$) prevalence of *S. stercoralis*, but the primary diagnostic method used, wet mount and formol-ethyl acetate concentration, is not ideal for *S. stercoralis* detection, so this study likely underestimated the true prevalence (Hung et al., 2019). Overall, infection due *S. stercoralis* appears to be more common, or at least is more commonly assessed, in the NT than in QLD or WA, and is much less prevalent in other states where autochthonous cases appear to be much rarer (Table 1). Eight papers focusing on QLD data, and three focusing on NSW data were identified in our literature search. The two most recent studies from QLD determined a *S. stercoralis* prevalence of 12% ($n=944$) by faecal examination and 30% ($n=867$) by serology in Woorabinda, and 6% ($n=695$) by PCR in the North Queensland health catchment area (Miller et al., 2018; Robertson et al., 2017).

A retrospective study investigating the rationale for HTLV-I serology testing in FNQ determined a HTLV-I prevalence of 0.98% ($n=409$), a *S. stercoralis* prevalence of 0.24%, and a *Sarcoptes scabiei* prevalence of 3% (Smith et al., 2019). The area covered extended from Innisfail to the Torres Strait in the North (Fig. 2). Only those individuals suspected of having HTLV-I were tested and having a positive diagnosis of strongyloidiasis or scabies was an indication for testing; only a few HTLV-I cases were identified. Although HTLV-I may have been present in other individuals, diagnostic testing was not undertaken. The three NSW reports were all case studies and at least one patient was likely infected on a trip to Central Australia (Fraser, 2019; Konecny et al., 2018; Walker-Smith et al., 1969). Fraser (2019) also reported a study where 32% (62/194) of adults from Aboriginal communities in coastal northern NSW were shown seropositive for *Strongyloides*.

In general, there seems to be a lack of recent community-wide studies of both HTLV-I and *Strongyloides* in Australia, and a dearth of publications of individual case studies, particularly in endemic areas. Fig. 2 depicts the distribution of HTLV-I and *S. stercoralis* from 1976 until 2019 and shows a much broader geographical spread of both pathogens, particularly with regard to WA and QLD. In the last 10 years there have been 20 papers identifying HTLV-I or *S. stercoralis* in Australian residents (Fig. 3 based on data from Supplementary Table 1 in the online version at <https://doi.org/10.1016/bs.apar.2020.11.002>). The majority of cases were observed in the NT, followed by FNQ and WA. The Alice Springs Hospital catchment area also captures some parts of South Australia and WA.

4.1.4 Locally acquired strongyloidiasis in non-aboriginal Australians

Strongyloidiasis is not unique to Aboriginal Australians as there are a number of reports of *S. stercoralis* infection in non-Aboriginal Australians. Eleven cases of locally acquired strongyloidiasis were identified in a Townsville hospital during the late 1980s of which three were Caucasian (Yiannakou et al., 1990). Of these, one individual was a former Australian Defence Force (ADF) member and may have acquired it while in service; all three case subjects were described to have been living in ‘insanitary’ conditions (Yiannakou et al., 1990). In a medical centre near Cairns in Queensland, in the 5 years between 2006 and 2011, 161 patients were positive or equivocal by serology; 108 were Aboriginal and 54 were non-Aboriginal (Beknazarova et al., 2018; Eager, 2011). A further four cases in those of Caucasian descent were identified in Alice Springs (Page et al., 2006; Soulsby et al., 2012), four from Darwin (Fisher et al., 1993), one from the NT (Mayer-Coverdale et al., 2017), and two from NQ (Yiannakou et al., 1990) (Table 1).



5. Immunology—Links between HTLV-I and *Strongyloides stercoralis* infection

In earlier studies it was initially thought that *Strongyloides* infection was a clinical sign of HTLV-I, much like certain infectious diseases can be diagnostic of HIV infection; indeed disseminated *Strongyloides* was also considered to be a sign of HIV although this has not turned out to be the case (Gompels et al., 1991; Lucas, 1990). The link between HTLV-I and *Strongyloides* co-infections is not clear-cut and there have been conflicting

reports of whether *Strongyloides* is more common in HTLV-I infected persons compared with those who are HTLV-I negative.

Helminth infections are often associated with a skewing of the immune response to a Th2 response and down regulation of inflammation (Turner et al., 2003). Both symptomatic and asymptomatic HTLV-I infections have been associated with an increase in pro-inflammatory cytokine production compared with HTLV-I-negative individuals. Studies in Brazil (Porto et al., 2005a; Santos et al., 2004) examined the cytokine levels in HTLV-I carriers and the relationship with helminth infection by either *S. stercoralis* or *Schistosoma mansoni* (Bezerra et al., 2018; Lima et al., 2019); *S. mansoni* is also endemic in Brazil and a common co-infection. A significant decrease in IFN- γ , a pro-inflammatory cytokine associated with HTLV-I infection, was recorded in helminth-infected individuals compared with those who were uninfected; however, this association was found to be greater in individuals harbouring *S. mansoni* than *S. stercoralis* (Porto et al., 2005a; Santos et al., 2004). Higher levels of IFN- γ were reported in HAM/TSP patients compared with 'asymptomatic' HTLV-I carriers, who in turn had significantly higher levels of the pro-inflammatory cytokine IFN- γ than HTLV-I-negative individuals (Santos et al., 2004). The pro-viral load was also significantly lower in helminth-infected individuals compared with those who were helminth-negative (Porto et al., 2005a). Another study found decreased levels of the pro-inflammatory cytokines TNF α and IFN- γ in *S. stercoralis*/HTLV-I co-infections compared with HTLV-I-only infections (Salles et al., 2013). After treatment with ivermectin for *S. stercoralis* infection TNF α levels increased (Salles et al., 2013). IFN- γ production was higher in the HTLV-I/helminth-co-infected individuals compared with those with helminth infection only (Porto et al., 2004). HTLV-I infection decreased the Th2 response normally observed in *S. stercoralis* infections (Porto et al., 2001a).

A study from Peru found a significant ($P < 0.05$) increase in the numbers of regulatory T-cells (T-regs) in *S. stercoralis*/HTLV-I co-infected individuals compared with subjects having *S. stercoralis* infection alone, and a significant ($P = 0.0004$) decrease in the anti-inflammatory cytokine IL-5 and eosinophil numbers in co-infections compared with *S. stercoralis* alone (Montes et al., 2009). Nematodes have been shown to induce the expansion of T-regs, which are a function of the ability of helminths to down-regulate inflammation. T-regs, particularly FoxP3 expressing T-regs, are associated with protecting the host from damage from inflammation through the release of inhibitory cytokines (Logan et al., 2018; Montes et al., 2009).

This response may be due to secretory/excretory molecules produced by helminth worms, or by alterations of the gut microbiome (Logan et al., 2018). In ATLL there is an increase in the expression of FoxP3 which may contribute to the immune suppression evident in HTLV-I infections (Montes et al., 2009). Thus, concurrent infections of *S. stercoralis* and HTLV-I may lead to a significant increase in Fox3P expression and T-regs, driven by both pathogens. This may lead to *Strongyloides* hyperinfection and dissemination, as well as the switch from asymptomatic HTLV-I to clinical HTLV-I. The immune response to either infection is not straightforward with many other interactions likely taking place. Lack of knowledge of other co-infections may also impact the outcomes of these types of studies, as well as the status of the HTLV-I infection.

Alcoholism has been associated with increased susceptibility to *Strongyloides* hyperinfection although this possible relationship has not been studied in Australia. A recent study in Brazil tested for strongyloidiasis in 345 patients admitted for alcoholism (De Souza et al., 2019). Both coproparasitological (spontaneous sedimentation, Baermann-Moraes, agar plate culture) and immunological (ELISA, immunoblotting) diagnostic techniques were used to assess prevalence determined as 21.4% (74/345) (De Souza et al., 2019). Five different anti-*S. stercoralis* antibody isotypes and subclasses (IgG, IgG1, IgG4, IgE and IgA1 anti-*S. stercoralis*) were tested in the ELISA, with some cross-reactivity evident in patients also infected with *S. mansoni* and hookworm; the IgE-ELISA proved the most sensitive and specific test for comparing alcoholic and non-alcoholic *S. stercoralis* infected individuals. However, in the alcoholic individuals the IgE-ELISA was negative in 30% of patients with larvae present in their faeces. Parasite load (assessed as *S. stercoralis* larvae per gram of faeces) was higher in those individuals testing negative by the IgE-ELISA compared with those who were IgE-ELISA positive; this suggested there was down regulation of IgE in alcoholic patients compared with non-alcoholic patients, with consequent impairment of eosinophil and mast cell function leading to *S. stercoralis* dissemination in these individuals (Carvalho and Da Fonseca Porto, 2004; De Souza et al., 2019). Other factors that may increase susceptibility to *S. stercoralis* hyperinfection in alcoholics include malnutrition, loss of intestinal mucosa integrity, reduction in intestinal motility, and poor hygiene (Teixeira et al., 2016). Several other studies identified alcoholism as a significant risk factor with higher frequency of *S. stercoralis* infection in alcoholics compared with non-alcoholics (de Oliveira et al., 2002; Marques et al., 2010; Schär et al., 2013; Teixeira et al., 2016). Indeed, in

several case studies of patients with *S. stercoralis* hyperinfection, alcoholism was the only identified risk factor (de Oliveira et al., 2002; Schär et al., 2013). Alcoholism has also been associated with an increase in *S. stercoralis* larvae identified in stool, providing a further indication that the infection becomes dysregulated (Marques et al., 2010).



6. Treatment of HTLV-I and *Strongyloides stercoralis*

While there is no cure for HTLV-I there are a number of treatments available to reduce disease severity and manage symptoms in those who are symptomatic. Opportunistic infections, including *Strongyloides* hyperinfection, are a hallmark of HTLV-I infection and they can be treated as they appear, although even targeted treatment of opportunistic infections can be complicated in HTLV-I cases (Tanaka et al., 2015).

There is no proven beneficial treatment for the HAM/TSP manifestation of HTLV-I, although the use of corticosteroids, blood purification, danazol, pentoxifylline, and interferon have all been suggested as potentially having long-term health benefits, although none of these studies are conclusive (Boostani et al., 2013; Nakagawa et al., 1996; Oh and Jacobson, 2008; Oh et al., 2005). Interferon- $\beta 1\alpha$ (IFN- $\beta 1\alpha$) was used to treat 12 patients with HAM/TSP over 28 weeks with increasing dosages from 30 $\mu\text{g}/\text{week}$ to 60 $\mu\text{g}/\text{twice weekly}$, and the subjects were followed for 12 weeks post treatment (Oh et al., 2005). Pro-viral loads did not change significantly and the Kurtzke expanded disability status scale (EDSS) remained relatively constant from baseline to post IFN- $\beta 1\alpha$ treatment. However, there was a significant ($P = 0.039$) decrease in transcriptional activity of HTLV-I, measured as a reduction in *tax* mRNA, after the treatment. There was also a significant decrease ($P = 0.003$) in spontaneous lympho-proliferation after treatment with IFN- $\beta 1\alpha$ (Oh et al., 2005). Overall, the results of this study indicated that IFN- $\beta 1\alpha$ may beneficially affect the immune mechanisms central to the pathogenesis of HAM/TSP reducing symptoms and pathology.

A case study utilizing IFN- $\beta 1\alpha$ found that treatment alleviated some of the symptoms of HAM/TSP, namely an improvement in paresthesia and motor skills after 4 weeks of treatment (IFN- $\beta 1\alpha$; 3,000,000 IU) (Viana et al., 2014). Another study from Iran reported on the effect of triple therapy (IFN- $\beta 1\alpha$ (180 $\mu\text{g}/\text{week}$); valproic acid (10–20 $\text{mg}/\text{kg}/\text{day}$); and prednisolone (5 mg/day)) on clinical outcomes of HAM/TSP in 13 patients; there was some, albeit non-significant, improvement in spasticity, reduction in

urinary disturbances, and a reduction in *tax* mRNA (Boostani et al., 2015). Methylprednisolone was used intravenously to treat an acute case of HAM/TSP with marked improvement in motor skills evidenced by the ability of the patient to walk without assistance 50 days posttreatment, although some sensory disturbances still remained (Boostani and Ghabeli Juibary, 2014).

Ivermectin is the recommended treatment for strongyloidiasis (Health, 2014; Page and Speare, 2016). A clinical trial on single vs multiple doses of ivermectin determined that a single treatment dose was better tolerated in those treated, with multiple doses not showing increased efficacy and that patients should be monitored to confirm successful treatment (Buonfrate et al., 2019). Despite the recorded efficacy of ivermectin treatment for *S. strongyloides* there have been cases documented of reduced efficacy of the drug, as determined by cure rates based on serological results, in persons co-infected with HTLV-I, a feature also observed with thiabendazole and albendazole (Carvalho and Da Fonseca Porto, 2004; Sato et al., 1994; Satoh et al., 2002).

A key point in the management of co-infection with HTLV-I and *S. stercoralis* is to recognize the danger of *Strongyloides* hyperinfection developing leading to high mortality and treating strongyloidiasis rapidly. In a number of case studies in Australia there was inadequate treatment of individuals for *S. stercoralis* co-infected with HTLV-I leading to patient mortality (Einsiedel and Fernandes, 2008; Einsiedel et al., 2016b).

6.1 Treatment failure against *Strongyloides stercoralis*

Although *S. stercoralis* is primarily treated with ivermectin, other anthelmintics including albendazole and thiabendazole have been used and are listed as available treatments by the WHO (WHO, 2019b). Ivermectin is considered the most effective drug as lower cure rates are evident with albendazole even after multi-day dosing (Marti et al., 1996; Suputtamongkol et al., 2011). Ivermectin is likewise used to treat scabies which is also endemic in Northern and Central Australia. Increased use of ivermectin for treatment of scabies may also be impacting on *Strongyloides* prevalence in Australia (Kearns et al., 2015; Marks et al., 2019). Unfortunately, while ivermectin is the preferred drug for treatment of strongyloidiasis, it may not be readily available in all countries.

Treatment failures with ivermectin, thiabendazole or albendazole against strongyloidiasis may be indicative of HTLV-I infection and these patients

should be tested for the presence of the virus (Sato et al., 2002; Terashima et al., 2002). Recurrent and relapsing strongyloidiasis was indicated in several case studies identified in this review, although this may have been due to re-infection rather than treatment failure (Table 2) (D’Incan et al., 1994; Gabet et al., 2003; Gessain et al., 1985; Patel et al., 2015; Phelps et al., 1991; Richter et al., 2005; Rio et al., 1990; Visy et al., 1993).

6.2 Anthelmintic resistance

Anthelmintic resistance in human *Strongyloides* infections has not been confirmed, but treatment failure with ivermectin, particularly in cases when confounding factors, such as immunosuppression or co-infections with other pathogens such as HTLV-I, are not present, have been identified in Australia (Hays et al., 2017a). Resistance to ivermectin has also been noted in scabies, although there are few studies available (Currie et al., 2004; Mounsey et al., 2008). In Australia use of ivermectin for scabies will also treat *Strongyloides* infection (Marks et al., 2019) but may also help select for resistance if used in programs of mass drug administration.

All drug classes used for the treatment of human helminth infections have resulted in resistance developing against helminths parasitic in animals (Coles et al., 2006; Kaplan, 2004), including the Family Strongylidae (Zak et al., 2017), to which *Strongyloides* spp. belong. Ivermectin resistance has been reported in a number of nematode parasites of livestock animals, while emerging ivermectin resistance has been reported in Africa against the human nematode *Onchocerca volvulus* (Abong et al., 2020; Osei-Atweneboana et al., 2011).

6.3 COVID-19

Recently case studies describing exacerbation of existing *Strongyloides* infection after steroid treatment (tocilizumab and dexamethasone) for COVID-19 in Italy and the USA have been published (Lier et al., 2020; Marchese et al., 2020). This has implications for treatment of COVID-19 in areas endemic for *Strongyloides*, and among immigrants and refugees in developed nations such as Australia and the USA (Lier et al., 2020). Stauffer et al. (2020) have presented a strategy for prevention of *Strongyloides* hyperinfection due to COVID-19 treatment with dexamethasone which includes pre-emptive treatment with ivermectin in those with moderate to high risk of *Strongyloides* infection who are also positive for the coronavirus.



7. Discussion and conclusion

Parasitic infections are generally considered as diseases of the tropics but it is important to note that the larvae of *S. stercoralis* can survive in temperatures down to 15 °C, and potentially lower. Indeed, one study demonstrated larval survival after 3 days at 4 °C (Ines Ede et al., 2011). Endemic areas for strongyloidiasis are typically located in tropical regions but transmission may also occur in temperate zones under certain conditions (Beknazarova et al., 2016; Strkolcova et al., 2017). Additionally, autoinfection and the potential for human–human and zoonotic transmission, as a result of poor hygiene practices and crowded housing, mean that it should be considered more as a cosmopolitan disease. In contrast, HTLV-I has no external phase and relies on human to human transmission and is thus not restricted to tropical and subtropical climates.

Australia is a developed nation with the only evidence of locally transmitted strongyloidiasis in areas of economic disadvantage that also coincide with a large Aboriginal Australian population (Beknazarova et al., 2016). HTLV-I and strongyloidiasis should not be regarded as unique diseases of Aboriginal Australians in Australia, but rather that these are diseases of disadvantage, as evident from both infections occurring in non-Aboriginal Australians (although at a much lower prevalence) and in many other parts of the world.

Since co-infection with HTLV-I and *S. stercoralis* can lead to severe disease it is recommended that HTLV-I-infected individuals with epidemiological risk of *S. stercoralis* infection should be tested for this parasite to prevent development of hyperinfection and disseminated disease. One of the issues surrounding the adequate treatment of these two pathogens in Australia is the lack of awareness of the potentially severe effects that can arise in co-infected patients. In many cases strongyloidiasis is either incorrectly diagnosed or when there is correct diagnosis inappropriate treatment is given or treatment is delayed. As indicated earlier, a strong case has been put forward to include strongyloidiasis on the list of notifiable diseases in Australia (Beknazarova et al., 2018). We fully endorse that request as this would help raise the profile of the disease and potentially increase successful identification and treatment of identified cases of strongyloidosis. In line with this, the development of education programs and accessibility to data for health professionals working in endemic areas and instructing new personnel when they arrive in Australia is also crucial to reinforce knowledge of HTLV-I

and *S. stercoralis*. Remote areas often have a high turnover of medical personnel and newly arrived doctors may have little knowledge or understanding of either pathogen, their immunological interactions, or the aetiology of the diseases they cause.

In addition to locally acquired infections, returned travellers infected with HTLV-I and *S. stercoralis* outside Australia also need careful monitoring. In particular, testing for both strongyloidiasis and HTLV of service personnel returning from endemic areas, and recent refugees and immigrants arriving from endemic areas is a major consideration. It is particularly important that clinicians consider possible *S. stercoralis* infection prior to prescribing immunosuppressive therapy, in order to prevent potentially fatal iatrogenic sequelae. Furthermore, there should be continued follow up of those who have tested positive for strongyloidiasis until successful seroreversion, as the duration of infection can last decades. This follow up should be undertaken on all patients who test positive, not only to ensure successful treatment, but also to monitor possible re-infection in patients at ongoing epidemiological risk posttreatment.

There is general consensus that strongyloidiasis is an under-reported disease. Large-scale screening is rarely performed, and the lack of knowledge about transmission and the potential role of zoonotic hosts in Australia hampers timely and effective diagnosis, treatment and control measures.

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References

- Abbott Prism HTLV-I/II Antigen (Inactivated). Abbott. <https://www.corelaboratory.abbott/int/en/offering/segments/infectious-disease>.
- Abe, T., 1986. Clinical, immunological, and virological aspects in Japanese hemophiliacs and AIDS patients. *AIDS Res.* 2 (Suppl. 1), S141–S146.
- Abong, R.A., Amambo, G.N., Ndongmo, P.W.C., Njouendou, A.J., Manuel, R., Beng, A.A., Esum, M.E., Deribe, K., Fru-Cho, J., Fombad, F.F., Nji, T.M., Enyong, P.I., Poole, C.B., Pfarr, K., Hoerauf, A., Carlow, C.K.S., Wanji, S., 2020. Differential susceptibility of *Onchocerca volvulus* microfilaria to ivermectin in two areas of contrasting history of mass drug administration in Cameroon: relevance of microscopy and molecular techniques for the monitoring of skin microfilarial repopulation within six months of direct observed treatment. *BMC Infect. Dis.* 20, 726.
- ABS, 2018a. 3238.0.55.001—Estimates of Aboriginal and Torres Strait Islander Australians, June 2016. Australia Bureau of Statistics.
- ABS, 2018b. Greater Darwin (GCCSA) (7GDAR).
- ABS, 2019. Migration, Australia, 2017–18.

- Adedayo, A.O., Grell, G.A., Bellot, P., 2001. Case study: fatal strongyloidiasis associated with human T-cell lymphotropic virus type 1 infection. *Am. J. Trop. Med. Hyg.* 65, 650–651.
- Adedayo, O., Grell, G., Bellot, P., 2002. Hyperinfective strongyloidiasis in the medical ward: review of 27 cases in 5 years. *South. Med. J.* 95, 711–716.
- Adedayo, O., Grell, G., Bellot, P., 2003. Hospital admissions for human T-cell lymphotropic virus type-1 (HTLV-1) associated diseases in dominica. *Postgrad. Med. J.* 79, 341–344.
- Adedayo, O., Nasiiro, R., 2004. Intestinal parasitoses. *J. Natl. Med. Assoc.* 96, 93–96.
- Agape, P., Copin, M.C., Cavois, M., Panelatti, G., Plumelle, Y., Ossondo-Landeanu, M., Quist, D., Grossat, N., Gosselin, B., Fenaux, P., Wattel, E., 1999. Implication of HTLV-I infection, strongyloidiasis, and P53 overexpression in the development, response to treatment, and evolution of non-Hodgkin's lymphomas in an endemic area (Martinique, French West Indies). *J. Acquir. Immune Defic. Syndr. Hum. Retrovirol.* 20, 394–402.
- Agut, H., Guetard, D., Collandre, H., Dauguet, C., Montagnier, L., Miclea, J.M., Baumann, H., Gessain, A., 1988. Concomitant infection by human herpesvirus 6, HTLV-I, and HIV-2. *Lancet (London, England)* 1, 712.
- Albarqi, M.M., Stoltzfus, J.D., Pilgrim, A.A., Nolan, T.J., Wang, Z., Kliwer, S.A., Mangelsdorf, D.J., Lok, J.B., 2016. Regulation of life cycle checkpoints and developmental activation of infective larvae in *Strongyloides stercoralis* by dafachronic acid. *PLoS Pathog.* 12, e1005358.
- Alpern, J.D., Arbefeille, S.S., Vercellotti, G., Ferrieri, P., Green, J.S., 2017. Strongyloides hyperinfection following hematopoietic stem cell transplant in a patient with HTLV-1-associated T-cell leukemia. *Transpl. Infect. Dis. Soc* 19. <https://doi.org/10.1111/tid.12638>.
- Alves, C., Dourado, L., 2010. Endocrine and metabolic disorders in HTLV-1 infected patients. *Braz. J. Infect. Dis.* 14, 613–620.
- Ando, Y., Matsumoto, Y., Nakano, S., Saito, K., Kakimoto, K., Tanigawa, T., Ekuni, Y., Kawa, M., Toyama, T., 2003. Long-term follow up study of vertical HTLV-I infection in children breast-fed by seropositive mothers. *J. Infect.* 46, 177–179.
- Ando, Y., Nakano, S., Saito, K., Shimamoto, I., Ichijo, M., Toyama, T., Hinuma, Y., 1987. Transmission of adult T-cell leukemia retrovirus (HTLV-I) from mother to child: comparison of bottle- with breast-fed babies. *Jpn. J. Cancer Res.* 78, 322–324.
- Ando, Y., Saito, K., Nakano, S., Kakimoto, K., Furuki, K., Tanigawa, T., Hashimoto, H., Moriyama, I., Ichijo, M., Toyama, T., 1989. Bottle-feeding can prevent transmission of HTLV-I from mothers to their babies. *J. Infect.* 19, 25–29.
- annardx, 2019. Murex.
- Anuradha, R., Munisankar, S., Bhootra, Y., Jagannathan, J., Dolla, C., Kumaran, P., Shen, K., Nutman, T.B., Babu, S., 2015. Systemic cytokine profiles in *Strongyloides stercoralis* infection and alterations following treatment. *Infect. Immun.* 84, 425–431.
- Arakaki, T., Asato, R., Ikeshiro, T., Sakiyama, K., Iwanaga, M., 1992a. Is the prevalence of HTLV-1 infection higher in Strongyloides carriers than in non-carriers? *Trop. Med. Parasitol.: official organ of Deutsche Tropenmedizinische Gesellschaft and of Deutsche Gesellschaft für Technische Zusammenarbeit (GTZ)*. 43, 199–200.
- Arakaki, T., Hasegawa, H., Asato, R., Ikeshiro, T., Kinjo, F., Saito, A., Iwanaga, M., 1988. A new method to detect *Strongyloides stercoralis* from human stool. *Jpn. J. Trop. Med. Hyg.* 16, 11–17.
- Arakaki, T., Kohakura, M., Asato, R., Ikeshiro, T., Nakamura, S., Iwanaga, M., 1992b. Epidemiological aspects of *Strongyloides stercoralis* infection in Okinawa, Japan. *J. Trop. Med. Hyg.* 95, 210–213.
- Aru, R.G., Chilcutt, B.M., Butt, S., deShazo, R.D., 2017. Novel findings in HIV, immune reconstitution disease and Strongyloides stercoralis infection. *Am. J. Med. Sci.* 353, 593–596.

- Ashford, R.W., Barnish, G., 1989. *Strongyloides* and hookworm in Papua New Guinea: longitudinal studies on treated and untreated children. *Ann. Trop. Med. Parasitol.* 83, 583–589.
- Ashford, R.W., Barnish, G., Viney, M.E., 1992. *Strongyloides fuelleborni kellyi*: infection and disease in Papua New Guinea. *Parasitol. Today (Personal ed.)* 8, 314–318.
- Atkins, N.S., Conway, D.J., Lindo, J.F., Bailey, J.W., Bundy, D.A., 1999. L3 antigen-specific antibody isotype responses in human strongyloidiasis: correlations with larval output. *Parasite Immunol.* 21, 517–526.
- Atkins, N.S., Lindo, J.F., Lee, M.G., Conway, D.J., Bailey, J.W., Robinson, R.D., Bundy, D.A., 1997. Humoral responses in human strongyloidiasis: correlations with infection chronicity. *Trans. R. Soc. Trop. Med. Hyg.* 91, 609–613.
- Australian Government, 1996. Determination of statement of principles concerning human T-cell lymphotropic virus tupe 1 (HTLV-1): veterans entitlements act 1986. In: *Legislation. F.r.o. (Ed.)*.
- Australian Government Department of Health, 2018. Funding to Combat Human T-Cell Lymphotropic Virus-1 in Remote Communities.
- Bandeira, L.M., Uehara, S.N.O., Puga, M.A.M., Rezende, G.R., Vicente, A.C.P., Domingos, J.A., do Lago, B.V., Niel, C., Motta-Castro, A.R.C., 2018. HTLV-1 intra-familial transmission among Japanese immigrants in Brazil. *J. Med. Virol.* 90, 351–357.
- Banerjee, P., Rochford, R., Antel, J., Canute, G., Wrzesinski, S., Sieburg, M., Feuer, G., 2007. Proinflammatory cytokine gene induction by human T-cell leukemia virus type 1 (HTLV-1) and HTLV-2 Tax in primary human glial cells. *J. Virol.* 81, 1690–1700.
- Barratt, J.L.N., Lane, M., Talundzic, E., Richins, T., Robertson, G., Formenti, F., Pritt, B., Verocai, G., Nascimento de Souza, J., Mato Soares, N., Traub, R., Buonfrate, D., Bradbury, R.S., 2019. A global genotyping survey of *Strongyloides stercoralis* and *Strongyloides fuelleborni* using deep amplicon sequencing. *PLoS Negl. Trop. Dis.* 13, e0007609.
- Barratt, J.L.N., Sapp, S.G.H., 2020. Machine learning-based analyses support the existence of species complexes for *Strongyloides fuelleborni* and *Strongyloides stercoralis*. *Parasitology* 147, 1184–1195.
- Barrett, J., 1968. The effect of temperature on the development and survival of the infective larvae of *Strongyloides ratti* Sandground, 1925. *Parasitology* 58, 641–651.
- Barros Kanzaki, L.L., 2006. Hypothetical HTLV-I induction by ionizing radiation. *Med. Hypotheses* 67, 177–182.
- Barros, N., Woll, F., Watanabe, L., Montes, M., 2012. Are increased Foxp3+ regulatory T cells responsible for immunosuppression during HTLV-1 infection? Case reports and review of the literature. *BMJ Case Rep.* 2012.
- Basile, A., Simzar, S., Bentow, J., Antelo, F., Shitabata, P., Peng, S.K., Craft, N., 2010. Disseminated *Strongyloides stercoralis*: hyperinfection during medical immunosuppression. *J. Am. Acad. Dermatol.* 63, 896–902.
- Bastian, I., Dent, J., McFarlane, R., Karopoulos, A., Way, B., 1993a. HTLV-I among Northern Territory blood donors. *Med. J. Aust.* 159, 7–12.
- Bastian, I., Gardner, J., Webb, D., Gardner, I., 1993b. Isolation of a human T-lymphotropic virus type I strain from Australian aboriginals. *J. Virol.* 67, 843–851.
- Bastian, I., Hinuma, Y., Doherty, R.R., 1993c. HTLV-I among Northern Territory aboriginals. *Med. J. Aust.* 159, 12–16.
- Bayley, A.C., Downing, R.G., Cheingsong-Popov, R., Tedder, R.S., Dalglish, A.G., Weiss, R.A., 1985. HTLV-III serology distinguishes atypical and endemic Kaposi's sarcoma in Africa. *Lancet (London, England)* 1, 359–361.
- Beknazarov, M., Barratt, J.L.N., Bradbury, R.S., Lane, M., Whiley, H., Ross, K., 2019. Detection of classic and cryptic *Strongyloides* genotypes by deep amplicon sequencing: a preliminary survey of dog and human specimens collected from remote Australian communities. *PLoS Negl. Trop. Dis.* 13, e0007241.

- Beknazarova, M., Whiley, H., Judd, J.A., Shield, J., Page, W., Miller, A., Whittaker, M., Ross, K., 2018. Argument for inclusion of Strongyloidiasis in the Australian national notifiable disease list. *Trop. Med. Infect. Dis.* 3, 61.
- Beknazarova, M., Whiley, H., Ross, K., 2016. Strongyloidiasis: a disease of socioeconomic disadvantage. *Int. J. Environ. Res. Public Health* 13, 517.
- Belongia, E.A., Holtan, N., MacDonald, K.L., Bowman, R.J., Osterholm, M.T., 1991. Absence of HTLV-1 infection in Southeast Asian refugees. *Southeast Asian J. Trop. Med. Public Health* 22, 135–136.
- Best, J.C., Welch, J.S., Filippich, C., McPhee, L., 1976. Treatment of intestinal parasites in Australian aboriginal children. *Med. J. Aust.* 1, 14–20.
- Bezerra, F.S.M., Leal, J.K.F., Sousa, M.S., Pinheiro, M.C.C., Ramos Jr., A.N., Silva-Moraes, V., Katz, N., 2018. Evaluating a point-of-care circulating cathodic antigen test (POC-CCA) to detect *Schistosoma mansoni* infections in a low endemic area in north-eastern Brazil. *Acta Trop.* 182, 264–270.
- Biddle, N., Markham, F., 2016. Census 2016: what's changed for Indigenous Australians? In: Ketchell, M. (Ed.), *The Conversation*.
- Biggs, B.A., Caruana, S., Mahrshahi, S., Jolley, D., Leydon, J., Chea, L., Nuon, S., 2009. Management of chronic strongyloidiasis in immigrants and refugees: is serologic testing useful? *Am. J. Trop. Med. Hyg.* 80, 788–791.
- Bisoffi, Z., Buonfrate, D., Montresor, A., Requena-Méndez, A., Muñoz, J., Krolewiecki, A.J., Gotuzzo, E., Mena, M.A., Chiodini, P.L., Anselmi, M., Moreira, J., Albonico, M., 2013. *Strongyloides stercoralis*: a plea for action. *PLoS Negl. Trop. Dis.* 7, e2214.
- Bisoffi, Z., Buonfrate, D., Sequi, M., Mejia, R., Cimino, R.O., Krolewiecki, A.J., Albonico, M., Gobbo, M., Bonafini, S., Angheben, A., Requena-Mendez, A., Munoz, J., Nutman, T.B., 2014. Diagnostic accuracy of five serologic tests for *Strongyloides stercoralis* infection. *PLoS Negl. Trop. Dis.* 8, e2640.
- Blank, A., Yamaguchi, K., Blank, M., Zaninovic, V., Sonoda, S., Takatsuki, K., 1993. Six Colombian patients with adult T-cell leukemia/lymphoma. *Leuk. Lymphoma* 9, 407–412.
- Boan, P., Swaminathan, R., Irish, A., 2017. Infectious complications in indigenous renal transplant recipients in Western Australia. *Intern. Med. J.* 47, 648–655.
- Bonin, S., Tothova, S.M., Barbazza, R., Brunetti, D., Stanta, G., Trevisan, G., 2010. Evidence of multiple infectious agents in mycosis fungoides lesions. *Exp. Mol. Pathol.* 89, 46–50.
- Boostani, R., Ghabeli Juibary, A., 2014. Acute human T-lymphotropic virus type I-associated myelitis: a rare case successfully treated with intravenous pulse methylprednisolone. *J. Neurovirol.* 20, 423–425.
- Boostani, R., Saber, H., Etemadi, M., 2013. Effects of danazol on clinical improvement of patients with human T-cell lymphotropic virus type I associated myelopathy/tropical spastic paraparesis (HAM/TSP): a placebo-controlled clinical trial. *Iran. J. Basic Med. Sci.* 16, 213–216.
- Boostani, R., Vakili, R., Hosseiny, S.S., Shoeibi, A., Fazeli, B., Etemadi, M.M., Sabet, F., Valizade, N., Rezaee, S.A., 2015. Triple therapy with prednisolone, pegylated interferon and sodium valproate improves clinical outcome and reduces human T-cell leukemia virus type 1 (HTLV-1) proviral load, Tax and HBZ mRNA expression in patients with HTLV-1-associated myelopathy/tropical spastic paraparesis. *Neurotherapeutics* 12, 887–895.
- Botterel, F., Cornet, M., Bouree, P., 1998. Incidental discovery of HTLV1 serology in recurrent strongyloidiasis: 2 cases. *Presse Med. (Paris, France)* 27, 1681.
- Boulos, R., Ruff, A.J., Nahmias, A., Holt, E., Harrison, L., Magder, L., Wiktor, S.Z., Quinn, T.C., Margolis, H., Halsey, N.A., 1992. Herpes simplex virus type 2 infection, syphilis, and hepatitis B virus infection in Haitian women with human immunodeficiency virus type 1 and human T lymphotropic virus type I infections. The Johns Hopkins University (JHU)/Centre pour le Developpement et la Sante (CDS) HIV Study Group. *J. Infect. Dis.* 166, 418–420.

- Bradbury, R., Thomas, A., 2006. Gastrointestinal parasites isolated from African refugees at the Royal Hobart Hospital 2002–2005. Australian Institute of Medical Scientists/ Australian Association of Clinical Biochemists National Scientific Meeting Hobart.
- Brown, R.C., Girardeau, H.F., 1977. Transmammary passage of *Strongyloides* sp. larvae in the human host. *Am. J. Trop. Med. Hyg.* 26, 215–219.
- Buchwald, D., Hooton, T.M., Ashley, R.L., 1992. Prevalence of herpesvirus, human T-lymphotropic virus type 1, and treponemal infections in Southeast Asian refugees. *J. Med. Virol.* 38, 195–199.
- Buonfrate, D., Requena-Mendez, A., Angheben, A., Munoz, J., Gobbi, F., Van Den Ende, J., Bisoffi, Z., 2013. Severe strongyloidiasis: a systematic review of case reports. *BMC Infect. Dis.* 13, 78.
- Buonfrate, D., Salas-Coronas, J., Munoz, J., Maruri, B.T., Rodari, P., Castelli, F., Zammarchi, L., Bianchi, L., Gobbi, F., Cabezas-Fernandez, T., Requena-Mendez, A., Godbole, G., Silva, R., Romero, M., Chiodini, P.L., Bisoffi, Z., 2019. Multiple-dose versus single-dose ivermectin for *Strongyloides stercoralis* infection (strong treat 1 to 4): a multicentre, open-label, phase 3, randomised controlled superiority trial. *Lancet Infect. Dis.*, 1181–1190.
- Byard, R.W., 2019. Lethal strongyloidiasis—diagnostic and forensic issues. *J. Forensic Leg. Med.* 62, 103–106.
- Campo Polanco, L., Gutiérrez, L.A., Cardona Arias, J., 2014. Diagnosis of *Strongyloides Stercoralis* infection: meta-analysis on evaluation of conventional parasitological methods (1980–2013). *Rev. Esp. Salud Publica* 88, 581–600.
- Cappell, M.S., Chow, J., 1987. HTLV-I-associated lymphoma involving the entire alimentary tract and presenting with an acquired immune deficiency. *Am. J. Med.* 82, 649–654.
- Caruana, S.R., Kelly, H.A., Ngeow, J.Y., Ryan, N.J., Bennett, C.M., Chea, L., Nuon, S., Bak, N., Skull, S.A., Biggs, B.A., 2006. Undiagnosed and potentially lethal parasite infections among immigrants and refugees in Australia. *J. Travel Med.* 13, 233–239.
- Carvalho, E.M., Da Fonseca Porto, A., 2004. Epidemiological and clinical interaction between HTLV-1 and *Strongyloides stercoralis*. *Parasite Immunol.* 26, 487–497.
- Cassar, O., Einsiedel, L., Afonso, P.V., Gessain, A., 2013. Human T-cell lymphotropic virus type 1 subtype C molecular variants among indigenous australians: new insights into the molecular epidemiology of HTLV-1 in Australo-Melanesia. *PLoS Negl. Trop. Dis.* 7, e2418.
- Caumes, E., Keystone, J.S., 2011. Acute strongyloidiasis: a rarity. Chronic strongyloidiasis: a time bomb! *J. Travel Med.* 18, 71–72.
- CDC, 1993. Guidelines for counseling persons infected with human T-lymphotropic virus type I (HTLV-I) and type II (HTLV-II). Centers for Disease Control and Prevention and the U.S.P.H.S. Working Group. *Ann. Intern. Med.* 118, 448–454.
- Chan, F.L.Y., Kennedy, B., Nelson, R., 2018. Fatal *Strongyloides* hyperinfection syndrome in an immunocompetent adult with review of the literature. *Intern. Med. J.* 48, 872–875.
- Chang, Y.T., Liu, H.N., Chen, C.L., Chow, K.C., 1998. Detection of Epstein-Barr virus and HTLV-I in T-cell lymphomas of skin in Taiwan. *Am. J. Dermatopathol.* 20, 250–254.
- Chaves, N.J., Gibney, K.B., Leder, K., O'Brien, D.P., Marshall, C., Biggs, B.-A., 2009. Screening practices for infectious diseases among Burmese refugees in Australia. *Emerg. Infect. Dis.* 15, 1769–1772.
- Chew, R., Henderson, T., Aujla, J., Whist, E., Einsiedel, L., 2018. Turning a blind eye: HTLV-1-associated uveitis in indigenous adults from Central Australia. *Int. Ophthalmol.* 38, 2159–2162.
- Chieffi, P.P., Chiattoni, C.S., Feltrim, E.N., Alves, R.C., Paschoalotti, M.A., 2000. Coinfection by *Strongyloides stercoralis* in blood donors infected with human T-cell leukemia/lymphoma virus type 1 in Sao Paulo City, Brazil. *Mem. Inst. Oswaldo Cruz* 95, 711–712.

- Clyti, E., Reynier, C., Couppie, P., Kazanji, M., Sainte-Marie, D., Prevost, G., Aznar, C., Pradinaud, R., 2004. Infective dermatitis and recurrent strongyloidiasis in a child. *Annales de dermatologie et de venerologie* 131, 191–193.
- Coles, G.C., Jackson, F., Pomroy, W.E., Prichard, R.K., von Samson-Himmelstjerna, G., Silvestre, A., Taylor, M.A., Vercruysse, J., 2006. The detection of anthelmintic resistance in nematodes of veterinary importance. *Vet. Parasitol.* 136, 167–185.
- Cordi, J.M., Otto, G.F., 1934. The effect of various temperatures on the eggs and larvae of *Strongyloides*. *Am. J. Epidemiol.* 19, 103–114.
- Courouble, G., Rouet, F., Hermann-Storck, C., Nicolas, M., Candolfi, E., Strobel, M., Carme, B., 2000. Human T-cell lymphotropic virus type I association with *Strongyloides stercoralis*: a case control study among Caribbean blood donors from Guadeloupe (French West Indies). *J. Clin. Microbiol.* 38, 3903–3904.
- Currie, B.J., Harumal, P., McKinnon, M., Walton, S.F., 2004. First documentation of in vivo and in vitro ivermectin resistance in *Sarcoptes scabiei*. *Clin. Infect. Dis.* 39, e8–e12.
- D'Incan, M., Combemale, P., Verrier, B., Garin, D., Audoly, G., Brunot, J., Desgranges, C., Flechaire, A., 1994. Transient adult T-cell leukemia/lymphoma picture during varicella infection in an HTLV-1 carrier. *Leukemia* 8, 682–687.
- da Silva Brito, V., Santos, F.L.N., 2018. Performance of commercially available serological screening tests for human T-cell lymphotropic virus infection in Brazil. *J. Clin. Microbiol.* 56, e00961-18.
- Davies, J., Jabbar, Z., Gagan, F., Baird, R.W., 2012. Blood-borne viruses in the haemodialysis-dependent population attending top end Northern Territory facilities 2000–2009. *Nephrology (Carlton, Vic.)* 17, 501–507.
- de Kaminsky, R.G., 1993. Evaluation of three methods for laboratory diagnosis of *Strongyloides stercoralis* infection. *J. Parasitol.* 79, 277–280.
- de Oliveira, C.J.V., Neto, J.A.C., Andrade, R.C.P., Rocha, P.N., de Carvalho Filho, E.M., 2017. Risk factors for erectile dysfunction in men with HTLV-1. *J. Sex. Med.* 14, 1195–1200.
- de Oliveira, L.C., Ribeiro, C.T., Mendes Dde, M., Oliveira, T.C., Costa-Cruz, J.M., 2002. Frequency of *Strongyloides stercoralis* infection in alcoholics. *Mem. Inst. Oswaldo Cruz* 97, 119–121.
- de Silva, S., Saykao, P., Kelly, H., MacIntyre, C.R., Ryan, N., Leydon, J., Biggs, B.A., 2002. Chronic *Strongyloides stercoralis* infection in Laotian immigrants and refugees 7–20 years after resettlement in Australia. *Epidemiol. Infect.* 128, 439–444.
- De Souza, J.N., Cruz, A.D.V., Araujo, W.A.C., Sampaio, L.M., Allegretti, S.M., Teixeira, M.C.A., Handali, S., Galvao-Castro, B., Soares, N.M., 2019. Alcohol consumption alters anti-*Strongyloides stercoralis* antibodies production. *Immunobiology*, 151898.
- Dixon, A.C., Yanagihara, E.T., Kwock, D.W., Nakamura, J.M., 1989. Strongyloidiasis associated with human T-cell lymphotropic virus type I infection in a nonendemic area. *West. J. Med.* 151, 410–413.
- Dooneief, G., Marlink, R., Bell, K., Marder, K., Renjifo, B., Stern, Y., Mayeux, R., 1996. Neurologic consequences of HTLV-II infection in injection-drug users. *Neurology* 46, 1556–1560.
- Dorris, M., Viney, M.E., Blaxter, M.L., 2002. Molecular phylogenetic analysis of the genus *Strongyloides* and related nematodes. *Int. J. Parasitol.* 32, 1507–1517.
- Dreyer, G., Fernandes-Silva, E., Alves, S., Rocha, A., Albuquerque, R., Addiss, D., 1996. Patterns of detection of *Strongyloides stercoralis* in stool specimens: implications for diagnosis and clinical trials. *J. Clin. Microbiol.* 34, 2569–2571.
- Dupin, M., Guennoc, B., Zimmermann, R., Martin, L., Verrier, B., Flechaire, A., Combemale, P., 1997. HTLV I virus infection disclosed by recurrent scabies associated with genital condylomatosis. *Ann. Med. Intern.* 148, 406–407.

- Eager, T., 2011. *Strongyloides* at Kuranda—an overview. In: 6th National Workshop on Strongyloidiasis. Pullman Reef Hotel, Cairns.
- Einsiedel, L., Cassar, O., Goeman, E., Spelman, T., Au, V., Hatami, S., Joseph, S., Gessain, A., 2014a. Higher human T-lymphotropic virus type 1 subtype c proviral loads are associated with bronchiectasis in Indigenous Australians: results of a case-control study. *Open Forum Infectious Diseases* 1, ofu023.
- Einsiedel, L., Cassar, O., Gordon, L., Gessain, A., 2013. Human T-lymphotropic virus type 1 infective dermatitis in central Australia. *Journal of Clinical Virology: The Official Publication of the Pan American Society for Clinical Virology* 57, 370–373.
- Einsiedel, L., Cassar, O., Spelman, T., Joseph, S., Gessain, A., 2016a. Higher HTLV-1c proviral loads are associated with blood stream infections in an Indigenous Australian population. *Journal of clinical virology: the official publication of the Pan American Society for Clinical Virology* 78, 93–98.
- Einsiedel, L., Fernandes, L., 2008. *Strongyloides stercoralis*: a cause of morbidity and mortality for indigenous people in Central Australia. *Intern. Med. J.* 38, 697–703.
- Einsiedel, L., Fernandes, L., Spelman, T., Steinfort, D., Gotuzzo, E., 2012. Bronchiectasis is associated with human T-lymphotropic virus 1 infection in an indigenous Australian population. *Clin. Infect. Dis.* 54, 43–50.
- Einsiedel, L., Pham, H., Wilson, K., Walley, R., Turpin, J., Bangham, C., Gessain, A., Woodman, R.J., 2018. Human T-lymphotropic virus type 1c subtype proviral loads, chronic lung disease and survival in a prospective cohort of Indigenous Australians. *PLoS Negl. Trop. Dis.* 12, e0006281.
- Einsiedel, L., Spelman, D., 2006. *Strongyloides stercoralis*: risks posed to immigrant patients in an Australian tertiary referral centre. *Intern. Med. J.* 36, 632–637.
- Einsiedel, L., Spelman, T., Goeman, E., Cassar, O., Arundell, M., Gessain, A., 2014b. Clinical associations of human T-lymphotropic virus type 1 infection in an indigenous Australian population. *PLoS Negl. Trop. Dis.* 8, e2643.
- Einsiedel, L., Woodman, R.J., Flynn, M., Wilson, K., Cassar, O., Gessain, A., 2016b. Human T-lymphotropic virus type 1 infection in an indigenous Australian population: epidemiological insights from a hospital-based cohort study. *BMC Public Health* 16, 787.
- Einsiedel, L.J., Pham, H., Woodman, R.J., Pepperill, C., Taylor, K.A., 2016c. The prevalence and clinical associations of HTLV-1 infection in a remote indigenous community. *Med. J. Aust.* 205, 305–309.
- Einsiedel, L.J., Woodman, R.J., 2010. Two nations: racial disparities in bloodstream infections recorded at Alice Springs Hospital, central Australia, 2001–2005. *Med. J. Aust.* 192, 567–571.
- Faull, M., Panegyres, P.K., 2014. A Caucasian Australian presenting with human T-lymphotropic virus type I associated myelopathy: a case report. *J. Med Case Rep.* 8, 382.
- Figueiro-Filho, E.A., Senefonte, F.R., Lopes, A.H., de Moraes, O.O., Souza Junior, V.G., Maia, T.L., Duarte, G., 2007. Frequency of HIV-1, rubella, syphilis, toxoplasmosis, cytomegalovirus, simple herpes virus, hepatitis B, hepatitis C, Chagas disease and HTLV I/II infection in pregnant women of State of Mato Grosso do Sul. *Rev. Soc. Bras. Med. Trop.* 40, 181–187.
- Fisher, D., McCarry, F., Currie, B., 1993. Strongyloidiasis in the Northern Territory. Under-recognised and under-treated? *Med. J. Aust.* 159, 88–90.
- Flannery, G., White, N., 1993. Immunological parameters in northeast Arnhem Land Aborigines: consequences of changing settlement patterns and lifestyles. In: Bilsborough, A., Schell, L.M., Smith, M. (Eds.), *Urban Ecology and Health in the Third World*. Cambridge University Press, Cambridge, pp. 202–220.
- Ford, J., Reiss-Levy, E., Clark, E., Dyson, A.J., Schonell, M., 1981. Pulmonary strongyloidiasis and lung abscess. *Chest* 79, 239–240.

- Foucan, L., Geneviev, I., Lamaury, I., Strobel, M., 1997. Aseptic purulent meningitis in two patients co-infected by HTLV-1 and *Strongyloides stercoralis*. *Med. Trop.* 57, 262–264.
- Fraser, J., 2019. A case report suggestive of strongyloidiasis infection occurring in temperate Australia. *Rural Remote Health* 19, 4787.
- Freedman, D.O., 1991. Experimental infection of human subject with *Strongyloides* species. *Rev. Infect. Dis.* 13, 1221–1226.
- Friedenberg, F., Wongpraparut, N., Fischer, R.A., Gubernick, J., Zaeri, N., Eiger, G., Ozden, Z., 1999. Duodenal obstruction caused by *Strongyloides stercoralis* enteritis in an HTLV-1-infected host. *Dig. Dis. Sci.* 44, 1184–1188.
- Fujii, N., Itoh, Y., Tomoda, H., 1993. Disseminated herpes zoster with multifocal neurologic involvement in an HTLV-1 carrier. *Intern. Med. (Tokyo, Japan)* 32, 854–856.
- Fujirebio, 2019. Serodia-HTLV-I.
- Funakawa, I., Shibata, A., Mukai, K., Terao, A., Niki, Y., 1993. A case of cryptococcal meningitis in an HTLV-1 carrier. *Rinsho shinkeigaku* 33, 895–900.
- Furuya, N., Shimozi, K., Nakamura, H., Owan, T., Tateyama, M., Tamaki, K., Fukuhara, H., Kusano, N., Shikiya, T., Kaneshima, H., et al., 1989. A case report of meningitis and sepsis due to *Enterococcus faecium* complicated with strongyloidiasis. *Kansenshogaku zasshi* 63, 1344–1349.
- Futsch, N., Mahieux, R., Dutartre, H., 2017. HTLV-1, the other pathogenic yet neglected human retrovirus: from transmission to therapeutic treatment. *Viruses* 10.
- Futsch, N., Prates, G., Mahieux, R., Casseb, J., Dutartre, H., 2018. Cytokine networks dysregulation during HTLV-1 infection and associated diseases. *Viruses* 10, 1.
- Gabet, A.S., Kazanji, M., Couppie, P., Clity, E., Pouliquen, J.F., Sainte-Marie, D., Aznar, C., Wattel, E., 2003. Adult T-cell leukaemia/lymphoma-like human T-cell leukaemia virus-1 replication in infective dermatitis. *Br. J. Haematol.* 123, 406–412.
- Gabet, A.S., Mortreux, F., Talarmin, A., Plumelle, Y., Leclercq, I., Leroy, A., Gessain, A., Clity, E., Joubert, M., Wattel, E., 2000. High circulating proviral load with oligoclonal expansion of HTLV-1 bearing T cells in HTLV-1 carriers with strongyloidiasis. *Oncogene* 19, 4954–4960.
- Gallo, R.C., 1988. Human retroviruses and herpes viruses: their role in immune dysfunctions and neoplasia. *Princess Takamatsu Symposia* 19, 31–43.
- Gallo, R.C., 2005. The discovery of the first human retrovirus: HTLV-1 and HTLV-2. *Retrovirology* 2, 17.
- Genta, R.M., 1992. Dysregulation of strongyloidiasis: a new hypothesis. *Clin. Microbiol. Rev.* 5, 345–355.
- Genta, R.M., Lillibridge, J.P., 1989. Prominence of IgG4 antibodies in the human responses to *Strongyloides stercoralis* infection. *J Infect Dis* 160, 692–699.
- Gessain, A., Cassar, O., 2012. Epidemiological aspects and world distribution of HTLV-1 Infection. *Front. Microbiol.* 3, 388.
- Gessain, A., Neisson-Vernant, C., Edouard, A., Calender, A., 1985. Recurring anguilluliasis and pleomorphic T lymphoma associated with anti-HTLV-I antibodies. *Presse Med. (Paris, France)* 14, 1610–1611.
- Gillet, N.A., Cook, L., Laydon, D.J., Hlela, C., Verdonck, K., Alvarez, C., Gotuzzo, E., Clark, D., Farre, L., Bittencourt, A., Asquith, B., Taylor, G.P., Bangham, C.R., 2013. Strongyloidiasis and infective dermatitis alter human T lymphotropic virus-1 clonality in vivo. *PLoS Pathog.* 9, e1003263.
- Gompels, M.M., Todd, J., Peters, B.S., Main, J., Pinching, A.J., 1991. Disseminated strongyloidiasis in AIDS: uncommon but important. *AIDS (London, England)* 5, 329–332.
- Gordon, C.A., Gray, D.J., Gobert, G.N., McManus, D.P., 2011. DNA amplification approaches for the diagnosis of key parasitic helminth infections of humans. *Mol. Cell. Probes* 25, 143–152.
- Gordon, C.A., McManus, D.P., Acosta, L.P., Olveda, R., Williams, M., Ross, A.G., Gray, D.J., Gobert, G.N., 2015. Multiplex real-time PCR monitoring of intestinal

- helminths in humans reveals widespread polyparasitism in Northern Samar, the Philippines. *Int. J. Parasitol.* 45, 477–483.
- Gotuzzo, E., Terashima, A., Alvarez, H., Tello, R., Infante, R., Watts, D.M., Freedman, D.O., 1999. *Strongyloides stercoralis* hyperinfection associated with human T cell lymphotropic virus type-1 infection in Peru. *Am. J. Trop. Med. Hyg.* 60, 146–149.
- Goubau, P., Desmyter, J., Swanson, P., Reynders, M., Shih, J., Surmont, I., Kazadi, K., Lee, H., 1993. Detection of HTLV-I and HTLV-II infection in Africans using type-specific envelope peptides. *J. Med. Virol.* 39, 28–32.
- Gracey, M., Sullivan, H., Burke, V., Wymer, V., Mogyrosy, R., Gunzburg, S., Iveson, J.B., 1992. Intestinal pathogens and parasites in Australian aboriginal children from birth to two years of age. *Trans. R. Soc. Trop. Med. Hyg.* 86, 222–223.
- Grant, K., Tiong, L.U., 2018. *Strongyloides stercoralis*: an unexpected cause of acute abdomen. *ANZ J. Surg.* 88, E456–e457.
- Grassi, M.F., Olavarria, V.N., Kruschewsky Rde, A., Mascarenhas, R.E., Dourado, I., Correia, L.C., de Castro-Costa, C.M., Galvao-Castro, B., 2011. Human T cell lymphotropic virus type 1 (HTLV-1) proviral load of HTLV-associated myelopathy/tropical spastic paraparesis (HAM/TSP) patients according to new diagnostic criteria of HAM/TSP. *J. Med. Virol.* 83, 1269–1274.
- Grivas, R., Freeman, K., Baird, R., 2014. Human T-lymphotropic virus-1 serology in the Northern Territory: 2008–2011. *Pathology* 46, 644–648.
- Gross, C., Thoma-Kress, A.K., 2016. Molecular mechanisms of HTLV-1 cell-to-cell transmission. *Viruses* 8, 74.
- Grove, D.I., 1980. Strongyloidiasis in allied ex-prisoners of war in south-east Asia. *Br. Med. J.* 280, 598–601.
- Grove, D.I., 1989. Clinical Manifestations. Taylor & Francis, London.
- Grove, D.I., 1990. A History of Human Helminthology. CAB International.
- Grove, D.I., Northern, C., 1982. Infection and immunity in dogs infected with a human strain of *Strongyloides stercoralis*. *Trans. R. Soc. Trop. Med. Hyg.* 76, 833–838.
- Guevara Miranda, J., Guzman Rojas, P., Espinoza-Rios, J., Mejia Cordero, F., 2017. Duodenal Lymphoma associated to *Strongyloides stercoralis* infection. Two types of HTLV-1 infection. *Rev. Gastroenterol. Peru* 37, 169–172.
- Guo, J., Sun, Y., Man, Y., Huang, X., Qin, Q., Zhou, D., Deng, A., 2015. Coinfection of *Strongyloides stercoralis* and *Aspergillus* found in bronchoalveolar lavage fluid from a patient with stubborn pulmonary symptoms. *J. Thorac. Dis.* 7, E43–E46.
- Gurry, G.A., Dendle, C., Woolley, I.J., 2015. Latent infection in HIV-positive refugees and other immigrants in Australia. *Med. J. Aust.* 202, ii–iii.
- Hanada, S., Uematsu, T., Iwahashi, M., Nomura, K., Utsunomiya, A., Kodama, M., Ishibashi, K., Terada, A., Saito, T., Makino, T., et al., 1989. The prevalence of human T-cell leukemia virus type I infection in patients with hematologic and nonhematologic diseases in an adult T-cell leukemia-endemic area of Japan. *Cancer* 64, 1290–1295.
- Hansen, E.L., Buecher, E.J., Cryan, W.S., 1969. *Strongyloides fülleborni*: environmental factors and free-living generations. *Exp. Parasitol.* 26, 336–343.
- Harrington Jr., W.J., Sheremata, W., Hjelle, B., Dube, D.K., Bradshaw, P., Fong, S.K., Snodgrass, S., Toedter, G., Cabral, L., Poesz, B., 1993. Spastic ataxia associated with human T-cell lymphotropic virus type II infection. *Ann. Neurol.* 33, 411–414.
- Hasegawa, H., Kalousova, B., McLennan, M.R., Modry, D., Profousova-Psenkova, I., Shutt-Phillips, K.A., Todd, A., Huffman, M.A., Petrzekova, K.J., 2016. *Strongyloides* infections of humans and great apes in Dzanga-Sangha protected areas, Central African Republic and in degraded forest fragments in Bulindi, Uganda. *Parasitol. Int.* 65, 367–370.
- Hayashi, J., Kishihara, Y., Yoshimura, E., Furusyo, N., Yamaji, K., Kawakami, Y., Murakami, H., Kashiwagi, S., 1997. Correlation between human T cell lymphotropic

- virus type-1 and *Strongyloides stercoralis* infections and serum immunoglobulin E responses in residents of Okinawa, Japan. *Am. J. Trop. Med. Hyg.* 56, 71–75.
- Hays, R., Esterman, A., McDermott, R., 2015. Type 2 diabetes mellitus is associated with *Strongyloides stercoralis* treatment failure in Australian aboriginals. *PLoS Negl. Trop. Dis.* 9, e0003976.
- Hays, R., Esterman, A., McDermott, R., 2017a. Control of chronic *Strongyloides stercoralis* infection in an endemic community may be possible by pharmacological means alone: results of a three-year cohort study. *PLoS Negl. Trop. Dis.* 11, e0005825.
- Hays, R., Giacomini, P., Olma, L., Esterman, A., McDermott, R., 2017b. The relationship between treatment for *Strongyloides stercoralis* infection and type 2 diabetes mellitus in an Australian Aboriginal population: a three-year cohort study. *Diabetes Res. Clin. Pract.* 134, 8–16.
- Healey, T., Selva-Nayagam, S., 2001. Retrospective review of febrile neutropenia in the Royal Darwin Hospital, 1994–99. *Intern. Med. J.* 31, 406–412.
- Health A.G.D.o., 2014. Ivermectin, 3 mg Tablets, Stromectol—March 2014.
- Heath, T., Riminton, S., Garsia, R., MacLeod, C., 1996. Systemic strongyloidiasis complicating HIV: a promising response to ivermectin. *Int. J. STD AIDS* 7, 294–296.
- Hedberg, S.T., Eriksson, L., Malm, K., Mölling, P., Sundqvist, M., Andersson, S., 2015. Droplet digital PCR for absolute quantification and determination of proviral load of HTLV-1 and 2. *Retrovirology* 12, 71.
- Higashirakawa, M., Hirata, T., Tanaka, T., Parrott, G., Kinjo, T., Naka, H., Hokama, A., Fujita, J., 2017. Normal serum IgE levels and eosinophil counts exhibited during *Strongyloides stercoralis* infection. *Parasitol. Int.* 66, 807–812.
- Higashiyama, Y., Sakata, H., Obase, Y., Sakata, S., Shimafuji, T., Mori, M., Ishino, T., Kohno, S., Saito, A., Hara, K., 1997. A case of bacterial meningitis induced by strongyloidiasis. *Kansenshogaku zasshi* 71, 680–683.
- Hino, S., Doi, H., Yoshikuni, H., Sugiyama, H., Ishimaru, T., Yamabe, T., Tsuji, Y., Miyamoto, T., 1987a. HTLV-I carrier mothers with high-titer antibody are at high risk as a source of infection. *Jpn. J. Cancer Res.* 78, 1156–1158.
- Hino, S., Sugiyama, H., Doi, H., 1986. Mother-to-child transmission of HTLV-I. *Nihon rinsho. Jpn. J. Clin. Med.* 44, 2283–2288.
- Hino, S., Sugiyama, H., Doi, H., Ishimaru, T., Yamabe, T., Tsuji, Y., Miyamoto, T., 1987b. Breaking the cycle of HTLV-I transmission via carrier mothers' milk. *Lancet (London, England)* 2, 158–159.
- Hino, S., Yamaguchi, K., Katamine, S., Sugiyama, H., Amagasaki, T., Kinoshita, K., Yoshida, Y., Doi, H., Tsuji, Y., Miyamoto, T., 1985. Mother-to-child transmission of human T-cell leukemia virus type-I. *Jpn. J. Cancer Res.* 76, 474–480.
- Hirata, T., Nakamura, H., Kinjo, N., Hokama, A., Kinjo, F., Yamane, N., Fujita, J., 2007. Increased detection rate of *Strongyloides stercoralis* by repeated stool examinations using the agar plate culture method. *Am. J. Trop. Med. Hyg.* 77, 683–684.
- Hirata, T., Uchima, N., Kishimoto, K., Zaha, O., Kinjo, N., Hokama, A., Sakugawa, H., Kinjo, F., Fujita, J., 2006. Impairment of host immune response against *strongyloides stercoralis* by human T cell lymphotropic virus type 1 infection. *Am. J. Trop. Med. Hyg.* 74, 246–249.
- Hiroyasu, S., Shiraishi, M., Shimabukuro, M., Kusano, T., Muto, Y., 1996. Adult T-cell leukemia/lymphoma with a giant gastric tumor: a case report. *Jpn. J. Clin. Oncol.* 26, 374–378.
- Hjelle, B., Appenzeller, O., Mills, R., Alexander, S., Torrez-Martinez, N., Jahnke, R., Ross, G., 1992. Chronic neurodegenerative disease associated with HTLV-II infection. *Lancet (London, England)* 339, 645–646.
- Holt, D.C., Shield, J., Harris, T.M., Mounsey, K.E., Aland, K., McCarthy, J.S., Currie, B.J., Kearns, T.M., 2017a. Soil-transmitted helminths in children in a remote Aboriginal

- community in the Northern Territory: hookworm is rare but *Strongyloides stercoralis* and *Trichuris trichiura* persist. *Trop. Med. Infect. Dis.* 2, 51.
- Holt, D.C., Shield, J., Harris, T.M., Mounsey, K.E., Aland, K., McCarthy, J.S., Currie, B.J., Kearns, T.M., 2017b. Soil-transmitted helminths in children in a remote Aboriginal Community in the Northern Territory: Hookworm is rare but *Strongyloides stercoralis* and *Trichuris trichiura* persist. *Trop. Med. Infect. Dis.* 2, e0005607.
- Honarbaksh, S., Taylor, G.P., 2015. High prevalence of bronchiectasis is linked to HTLV-1-associated inflammatory disease. *BMC Infect. Dis.* 15, 258.
- Hoque, S., Kelsey, S., van der Walt, J.D., Breuer, J., 1996. Experience of human lymphotropic virus type I (HTLV-I) in an East London hospital. *J. Infect.* 32, 33–39.
- Hovette, P., Tuan, J.F., Camara, P., Lejean, Y., Lo, N., Colbacchini, P., 2002. Pulmonary strongyloidiasis complicated by *E. coli* meningitis in a HIV-1 and HTLV-1 positive patient. *Presse Med. (Paris, France: 1983)* 31, 1021–1023.
- HTLV-Aware, 2018. Alice Springs Collaborative Forum on HTLV-1: August 2018.
- Hung, T.Y., Janson, S., Smith, P., Legg, A., Baird, R.W., 2019. Declining soil transmitted helminth detections in an Australian tropical region. *Pathology* 51, 737–741.
- Hunter, M., Beltramino, S., Vera Ocampo, C., Sanchez Marull, R., Badariotti, G., De Diego, B., 2019. *Strongyloides* hyperinfection in patient from Patagonia with HTLV-1 co-infection. *Medicina* 79, 147–149.
- Hutchinson, P., 2003. Strongyloidiasis: An Investigation Into Prevalence. Second National Strongyloidiasis Workshop, Brisbane.
- Ikeda, F., Haraguchi, Y., Jinno, A., Iino, Y., Morishita, Y., Shiraki, H., Hoshino, H., 1998. Human complement component C1q inhibits the infectivity of cell-free HTLV-I. *J. Immunol. (Baltimore, Md.: 1950)* 161, 5712–5719.
- Ines Ede, J., Souza, J.N., Santos, R.C., Souza, E.S., Santos, F.L., Silva, M.L., Silva, M.P., Teixeira, M.C., Soares, N.M., 2011. Efficacy of parasitological methods for the diagnosis of *Strongyloides stercoralis* and hookworm in faecal specimens. *Acta Trop.* 120, 206–210.
- Isotalo, P.A., Toye, B., Eidus, L., 2000. Human T-lymphotropic virus 1 adult T-cell lymphoma with *Giardia* and *Strongyloides* parasitism. *Arch. Pathol. Lab. Med.* 124, 1241.
- Jacobson, S., Lehy, T., Nishimura, M., Robinson, S., McFarlin, D.E., Dhib-Jalbut, S., 1993. Isolation of HTLV-II from a patient with chronic, progressive neurological disease clinically indistinguishable from HTLV-I-associated myelopathy/tropical spastic paraparesis. *Ann. Neurol.* 33, 392–396.
- Jaleta, T.G., Zhou, S., Bemm, F.M., Schär, F., Khieu, V., Muth, S., Odermatt, P., Lok, J.B., Streit, A., 2017. Different but overlapping populations of *Strongyloides stercoralis* in dogs and humans—dogs as a possible source for zoonotic strongyloidiasis. *PLoS Negl. Trop. Dis.* 11, e0005752.
- Jex, A.R., Lim, Y.A., Bethony, J.M., Hotez, P.J., Young, N.D., Gasser, R.B., 2011. Soil-transmitted helminths of humans in Southeast Asia—towards integrated control. *Adv. Parasitol.* 74, 231–265.
- Jones, H.I., 1980. Intestinal parasite infections in Western Australian Aborigines. *Med. J. Aust.* 2, 375–380.
- Kajiyama, W., Kashiwagi, S., Ikematsu, H., Hayashi, J., Nomura, H., Okochi, K., 1986. Intrafamilial transmission of adult T cell leukemia virus. *J. Infect. Dis.* 154, 851–857.
- Kakazu, T., Saito, A., Chihara, J., Nakajima, S., 1996. Expression of CD23, CD32, Mac-1 and other adhesion molecules in eosinophils in strongyloidiasis and HTLV-I-positive patients. *Int. Arch. Allergy Immunol.* 111 (Suppl 1), 46–50.
- Kaplan, R.M., 2004. Drug resistance in nematodes of veterinary importance: a status report. *Trends Parasitol.* 20, 477–481.
- Kawano, Y., Kira, J., 1995. Chronic hypertrophic cranial pachymeningitis associated with HTLV-I infection. *J. Neurol. Neurosurg. Psychiatry* 59, 435–437.

- Kearns, T.M., Currie, B.J., Cheng, A.C., McCarthy, J., Carapetis, J.R., Holt, D.C., Page, W., Shield, J., Gundjirryirr, R., Mulholland, E., Ward, L., Andrews, R.M., 2017. *Strongyloides* seroprevalence before and after an ivermectin mass drug administration in a remote Australian Aboriginal community. *PLoS Negl. Trop. Dis.* 11, e0005607.
- Kearns, T.M., Speare, R., Cheng, A.C., McCarthy, J., Carapetis, J.R., Holt, D.C., Currie, B.J., Page, W., Shield, J., Gundjirryirr, R., Bundhala, L., Mulholland, E., Chatfield, M., Andrews, R.M., 2015. Impact of an ivermectin mass drug administration on Scabies prevalence in a remote Australian aboriginal community. *PLoS Negl. Trop. Dis.* 9, e0004151.
- Kelly, A., Little, M.D., Voge, M., 1976. *Strongyloides fulleborni*-like infections in man in Papua New Guinea. *Am. J. Trop. Med. Hyg.* 25, 694–699.
- Kennedy, S., Campbell, R.M., Lawrence, J.E., Nichol, G.M., Rao, D.M., 1989. A case of severe *Strongyloides stercoralis* infection with jejunal perforation in an Australian ex-prisoner-of-war. *Med. J. Aust.* 150, 92–93.
- Khieu, V., Schar, F., Marti, H., Sayasone, S., Duong, S., Muth, S., Odermatt, P., 2013. Diagnosis, treatment and risk factors of *Strongyloides stercoralis* in schoolchildren in Cambodia. *PLoS Negl. Trop. Dis.* 7, e2035.
- King, S.E., Mascie-Taylor, C.G., 2004. *Strongyloides fuelleborni kellyi* and other intestinal helminths in children from Papua New Guinea: associations with nutritional status and socioeconomic factors. *Papua New Guinea Med. J.* 47, 181–191.
- Kinoshita, K., Amagasaki, T., Hino, S., Doi, H., Yamanouchi, K., Ban, N., Momita, S., Ikeda, S., Kamihira, S., Ichimaru, M., et al., 1987. Milk-borne transmission of HTLV-I from carrier mothers to their children. *Jpn. J. Cancer Res. Gann.* 78, 674–680.
- Kinoshita, K., Hino, S., Amagasaki, T., Ikeda, S., Yamada, Y., Suzuyama, J., Momita, S., Toriya, K., Kamihira, S., Ichimaru, M., 1984. Demonstration of adult T-cell leukemia virus antigen in milk from three sero-positive mothers. *Gann* 75, 103–105.
- Kirkland, M.A., Frasca, J., Bastian, I., 1991. Adult T-cell leukaemia lymphoma in an aborigine. *Aust. N. Z. J. Med.* 21, 739–741.
- Knopp, S., Salim, N., Schindler, T., Karagiannis Voules, D.A., Rothen, J., Lweno, O., Mohammed, A.S., Singo, R., Benninghoff, M., Nsojo, A.A., Genton, B., Daubenberger, C., 2014. Diagnostic accuracy of Kato-Katz, FLOTAC, Baermann, and PCR methods for the detection of light-intensity hookworm and *Strongyloides stercoralis* infections in Tanzania. *Am. J. Trop. Med. Hyg.* 90, 535–545.
- Koga, K., Kasuya, S., Khamboonruang, C., Sukavat, K., Nakamura, Y., Tani, S., Ieda, M., Tomita, K., Tomita, S., Hattan, N., et al., 1990. An evaluation of the agar plate method for the detection of *Strongyloides stercoralis* in northern Thailand. *J. Trop. Med. Hyg.* 93, 183–188.
- Konecny, P., Weatherall, C.J., Adhikari, S., Duflou, J., Marjoniemi, V., Pretorius, C.J., McWhinney, B., 2018. Case report: subcutaneous ivermectin pharmacokinetics in disseminated *Strongyloides* infection: plasma and postmortem analysis. *Am. J. Trop. Med. Hyg.* 99, 1580–1582.
- Koyanagi, Y., Itoyama, Y., Nakamura, N., Takamatsu, K., Kira, J., Iwamasa, T., Goto, I., Yamamoto, N., 1993. In vivo infection of human T-cell leukemia virus type I in non-T cells. *Virology* 196, 25–33.
- Lambertucci, J.R., Leao, F.C., Barbosa, A.J., 2003. Gastric strongyloidiasis and infection by the human T cell lymphotropic virus type 1 (HTLV-1). *Rev. Soc. Bras. Med. Trop.* 36, 541–542.
- Li, H.C., Biggar, R.J., Miley, W.J., Maloney, E.M., Cranston, B., Hanchard, B., Hisada, M., 2004. Provirus load in breast milk and risk of mother-to-child transmission of human T lymphotropic virus type I. *J Infect Dis* 190, 1275–1278.
- Lier, A.J., Tuan, J.J., Davis, M.W., Paulson, N., McManus, D., Campbell, S., Peaper, D.R., Topal, J.E., 2020. Case report: disseminated strongyloidiasis in a patient with COVID-19. *Am. J. Trop. Med. Hyg.* 103, 1590–1592.

- Lim, L., Biggs, B.A., 2001. Fatal disseminated strongyloidiasis in a previously treated patient. *Med. J. Aust.* 174, 355–356.
- Lima, J.P., Delgado, P.G., 1961. Diagnosis of strongyloidiasis: importance of Baermann's method. *Am. J. Dig. Dis.* 6, 899–904.
- Lima, M.G., Montresor, L.C., Pontes, J., Augusto, R.C., da Silva, J.P., Thiengo, S.C., 2019. Compatibility polymorphism based on long-term host-parasite relationships: cross talking between *biomphalaria glabrata* and the trematode *schistosoma mansoni* from endemic areas in Brazil. *Front. Immunol.* 10, 328.
- Logan, J., Navarro, S., Loukas, A., Giacomini, P., 2018. Helminth-induced regulatory T cells and suppression of allergic responses. *Curr. Opin. Immunol.* 54, 1–6.
- Luca, D.C., August, C.Z., Weisenberg, E., 2003. Adult T-cell leukemia/lymphoma in a peripheral blood smear. *Arch. Pathol. Lab. Med.* 127, 636.
- Lucas, S.B., 1990. Missing infections in AIDS. *Trans. R. Soc. Trop. Med. Hyg.* 84 (Suppl. 1), 34–38.
- Ly, M.N., Bethel, S.L., Usmani, A.S., Lambert, D.R., 2003. Cutaneous *Strongyloides stercoralis* infection: an unusual presentation. *J. Am. Acad. Dermatol.* 49, S157–S160.
- Malezieux-Picard, A., Saint-Paul, M.C., Dellamonica, J., Courjon, J., Tieulie, N., Marty, P., Fuzibet, J.G., Collomp, R., Marinho, J.A., Queyrel, V., 2017. Severe intestinal obstruction due to *Strongyloides stercoralis* in a pregnant woman. *Med. Mal. Infect.* 47, 429–431.
- Marchese, V., Crosato, V., Gulletta, M., Castelnuovo, F., Cristini, G., Matteelli, A., Castelli, F., 2020. *Strongyloides* infection manifested during immunosuppressive therapy for SARS-CoV-2 pneumonia. *Infection*, 1–4. <https://doi.org/10.1007/s15010-020-01522-4>.
- Marcos, L.A., Terashima, A., Canales, M., Gotuzzo, E., 2011. Update on strongyloidiasis in the immunocompromised host. *Curr. Infect. Dis. Rep.* 13, 35–46.
- Marks, M., Gwyn, S., Toloka, H., Kositz, C., Asugeni, J., Asugeni, R., Diau, J., Kaldor, J., Romani, L., Redman-MacLaren, M., MacLaren, D., Solomon, A., Mabey, D., Steer, A., Martin, D., 2019. Impact of community treatment with ivermectin for the control of scabies on the prevalence of antibodies to *Strongyloides stercoralis* in children. *Clinical Infectious Diseases*, ciaa584.
- Marques, C.C., da Penha Zago-Gomes, M., Goncalves, C.S., Pereira, F.E., 2010. Alcoholism and *Strongyloides stercoralis*: daily ethanol ingestion has a positive correlation with the frequency of *Strongyloides* larvae in the stools. *PLoS Negl. Trop. Dis.* 4, e717.
- Marr, I., Davies, J., Baird, R.W., 2017. Hepatitis B virus and human T-cell lymphotropic virus type 1 co-infection in the Northern Territory, Australia. *Int. J. Infect. Dis.* 58, 90–95.
- Marti, H., Haji, H.J., Savioli, L., Chwaya, H.M., Mgeni, A.F., Ameir, J.S., Hatz, C., 1996. A comparative trial of a single-dose ivermectin versus three days of albendazole for treatment of *Strongyloides stercoralis* and other soil-transmitted helminth infections in children. *Am. J. Trop. Med. Hyg.* 55, 477–481.
- Mascarello, M., Gobbi, F., Angheben, A., Gobbo, M., Gaiera, G., Pegoraro, M., Lanzafame, M., Buonfrate, D., Concia, E., Bisoffi, Z., 2011. Prevalence of *Strongyloides stercoralis* infection among HIV-positive immigrants attending two Italian hospitals, from 2000 to 2009. *Ann. Trop. Med. Parasitol.* 105, 617–623.
- Massey, A.C., Weinstein, D.L., Petri, W.A., Williams, M.E., Hess, C.E., 1990. ATLL complicated by strongyloidiasis and isosporiasis: case report. *Va. Med. Q.* 117, 311–316.
- Matsuura, E., Nozuma, S., Tashiro, Y., Kubota, R., Izumo, S., Takashima, H., 2016. HTLV-1 associated myelopathy/tropical spastic paraparesis (HAM/TSP): A comparative study to identify factors that influence disease progression. *J. Neurol. Sci.* 371, 112–116.
- May, J.T., Stent, G., Bishop, F., Schnagl, D., 1990. Prevalence of antibody to human T-lymphotropic virus type-1 (HTLV-1) in Australian aborigines, and detection in Indonesian sera. *Acta Virol.* 34, 80–84.

- Mayer-Coverdale, J.K., Crowe, A., Smith, P., Baird, R.W., 2017. Trends in *Strongyloides stercoralis* faecal larvae detections in the Northern Territory, Australia: 2002 to 2012. *Trop. Med. Infect. Dis.* 2 (2), 18.
- Mejia, R., Nutman, T.B., 2012. Screening, prevention, and treatment for hyperinfection syndrome and disseminated infections caused by *Strongyloides stercoralis*. *Curr. Opin. Infect. Dis.* 25, 458–463.
- Meloni, B.P., Thompson, R.C., Hopkins, R.M., Reynoldson, J.A., Gracey, M., 1993. The prevalence of *Giardia* and other intestinal parasites in children, dogs and cats from aboriginal communities in the Kimberley. *Med. J. Aust.* 158, 157–159.
- Menz, F., Menz, J., Wilson, K., Turpin, J., Bangham, C., Einsiedel, L., 2018. Infective dermatitis associated with human T-lymphotropic virus type 1 infection in Adelaide, South Australia. *Australas. J. Dermatol.* 59, 151–153.
- Miller, A., Young, E.L., Tye, V., Cody, R., Muscat, M., Saunders, V., Smith, M.L., Judd, J.A., Speare, R., 2018. A community-directed integrated *Strongyloides* control program in Queensland, Australia. *Trop. Med. Infect. Dis.* 3 (2), 48.
- Mitsunaga, M., Miyauchi, N., Akiyama, Y., Saima, S., 2003. A case of strongyloidiasis hyperinfection during oral corticosteroid therapy associated with a nephrotic patient infected with HTLV-1. *Nihon Ronen Igakkai zasshi. Jpn. J. Geriatr.* 40, 397–401.
- Mollison, L.C., 1994. HTLV-I and clinical disease correlates in central Australian aborigines. *Med. J. Aust.* 160, 238.
- Mollison, L.C., Lo, S.T., Marning, G., 1993. HTLV-I and scabies in Australian aborigines. *Lancet (London, England)* 341, 1281–1282.
- Montes, M., Sanchez, C., Verdonck, K., Lake, J.E., Gonzalez, E., Lopez, G., Terashima, A., Nolan, T., Lewis, D.E., Gotuzzo, E., White Jr., A.C., 2009. Regulatory T cell expansion in HTLV-1 and strongyloidiasis co-infection is associated with reduced IL-5 responses to *Strongyloides stercoralis* antigen. *PLoS Negl. Trop. Dis.* 3, e456.
- Montes, M., Sawhney, C., Barros, N., 2010. *Strongyloides stercoralis*: there but not seen. *Curr. Opin. Infect. Dis.* 23, 500–504.
- Mounsey, K., Kearns, T., Rampton, M., Llewellyn, S., King, M., Holt, D., Currie, B.J., Andrews, R., Nutman, T., McCarthy, J., 2014. Use of dried blood spots to define antibody response to the *Strongyloides stercoralis* recombinant antigen NIE. *Acta Trop.* 138, 78–82.
- Mounsey, K.E., Holt, D.C., McCarthy, J., Currie, B.J., Walton, S.F., 2008. Scabies: molecular perspectives and therapeutic implications in the face of emerging drug resistance. *Future Microbiol.* 3, 57–66.
- Mukaigawara, M., Nakayama, I., Gibo, K., 2018. Strongyloidiasis and culture-negative suppurative meningitis, Japan, 1993–2015. *Emerg. Infect. Dis.* 24, 2378–2380.
- Mukerjee, C.M., Carrick, J., Walker, J.C., Woods, R.L., 2003. Pulmonary strongyloidiasis presenting as chronic bronchitis leading to interlobular septal fibrosis and cured by treatment. *Respirology (Carlton, Vic.)* 8, 536–540.
- Murphy, E.L., Fridey, J., Smith, J.W., Engstrom, J., Sacher, R.A., Miller, K., Gible, J., Stevens, J., Thomson, R., Hansma, D., Kaplan, J., Khabbaz, R., Nemo, G., 1997. HTLV-associated myelopathy in a cohort of HTLV-I and HTLV-II-infected blood donors. The REDS investigators. *Neurology* 48, 315–320.
- Nagayasu, E., Aung, M., Hortiwakul, T., Hino, A., Tanaka, T., Higashiarakawa, M., Oia, A., Taniguchi, T., Win, S.M.T., Ohashi, I., Odongo-Aginya, E.I., Aye, K.M., Mon, M., Win, K.K., Ota, K., Torisu, Y., Panthuwong, S., Kimura, E., Palacpac, N.M.Q., Kikuchi, T., Hirata, T., Torisu, S., Hisaeda, H., Horii, T., Fujita, J., Htike, W.W., Maruyama, H., 2017. A possible origin population of pathogenic intestinal nematodes, *Strongyloides stercoralis*, unveiled by molecular phylogeny. *Sci. Rep.* 7, 4844.

- Nakada, K., Yamaguchi, K., Furugen, S., Nakasone, T., Nakasone, K., Oshiro, Y., Kohakura, M., Hinuma, Y., Seiki, M., Yoshida, M., et al., 1987. Monoclonal integration of HTLV-I proviral DNA in patients with strongyloidiasis. *Int. J. Cancer* 40, 145–148.
- Nakada, T., Knight, R.T., 1984. Alcohol and the central nervous system. *Med. Clin. North Am.* 68, 121–131.
- Nakagawa, M., Nakahara, K., Maruyama, Y., Kawabata, M., Higuchi, I., Kubota, H., Izumo, S., Arimura, K., Osame, M., 1996. Therapeutic trials in 200 patients with HTLV-I-associated myelopathy/tropical spastic paraparesis. *J. Neurovirol.* 2, 345–355.
- Nakamura, N., Matsushita, M., Tahashi, Y., Shimatani, M., Aoi, K., Yanagawa, M., Okazaki, K., 2010. Diagnostic yield of double-balloon enteroscopy with intestinal juice analysis for intestinal strongyloidiasis. *Dig. Endosc.* 22, 370–372.
- Nayar, S., Pawar, B., Einsiedel, L., Fernandes, D., George, P., Thomas, S., Sajiv, C., 2018. Isolated neurogenic bladder associated with human T-lymphotropic virus type 1 infection in a renal transplant patient from Central Australia: a case report. *Transplant. Proc.* 50, 3940–3942.
- Neva, F.A., Filho, J.O., Gam, A.A., Thompson, R., Freitas, V., Melo, A., Carvalho, E.M., 1998. Interferon-gamma and interleukin-4 responses in relation to serum IgE levels in persons infected with human T lymphotropic virus type I and *Strongyloides stercoralis*. *J. Infect. Dis.* 178, 1856–1859.
- Newton, R.C., Limpuangthip, P., Greenberg, S., Gam, A., Neva, F.A., 1992. *Strongyloides stercoralis* hyperinfection in a carrier of HTLV-I virus with evidence of selective immunosuppression. *Am. J. Med.* 92, 202–208.
- Ngo, C.C., Maidment, C., Atkins, L., Eagar, S., Smith, M.M., 2018. Blood screen findings in a 2-year cohort of newly arrived refugees to Sydney, Australia. *Public Health Res. Pract.* 28, 2811804.
- Nicholson, S.R., Efandis, T., Dimitrakakis, M., Karopoulos, A., Lee, H., Gust, I.D., 1992. HTLV-I infection in selected populations in Australia and the western Pacific region. *Med. J. Aust.* 156, 878–880.
- Nicolas, M., Perez, J.M., Carme, B., 2006. Intestinal parasitosis in French West Indies: endemic evolution from 1991 to 2003 in the University Hospital of Pointe-à-Pitre, Guadeloupe. *Bulletin de la Societe de pathologie exotique* (1990) 99, 254–257.
- Nonaka, D., Takaki, K., Tanaka, M., Umeno, M., Takeda, T., Yoshida, M., Haraguch, Y., Okada, K., Sawae, Y., 1998. Paralytic ileus due to strongyloidiasis: case report and review of the literature. *Am. J. Trop. Med. Hyg.* 59, 535–538.
- NORD, 2019. HTLV Type I and Type II.
- Norsyahida, A., Riaz, M., Sadjjadi, S.M., Muhammad Hafiznur, Y., Low, H.C., Zeehaida, M., Noordin, R., 2013. Laboratory detection of strongyloidiasis: IgG-, IgG4- and IgE-ELISAs and cross-reactivity with lymphatic filariasis. *Parasite Immunol.* 35, 174–179.
- Nutman, T.B., 2017. Human infection with *Strongyloides stercoralis* and other related Strongyloides species. *Parasitology* 144, 263–273.
- Oh, U., Jacobson, S., 2008. Treatment of HTLV-I-associated myelopathy/tropical spastic paraparesis: toward rational targeted therapy. *Neurol. Clin.* 26, 781–797. ix–x.
- Oh, U., Yamano, Y., Mora, C.A., Ohayon, J., Bagnato, F., Butman, J.A., Dambrosia, J., Leist, T.P., McFarland, H., Jacobson, S., 2005. Interferon-beta1a therapy in human T-lymphotropic virus type I-associated neurologic disease. *Ann. Neurol.* 57, 526–534.
- Oliveira, P., Castro, N.M., Carvalho, E.M., 2007. Urinary and sexual manifestations of patients infected by HTLV-I. *Clinics (Sao Paulo, Brazil)* 62, 191–196.
- Oliveira, P.D., Kachimarek, A.C., Bittencourt, A.L., 2018. Early onset of HTLV-1 associated myelopathy/tropical spastic paraparesis (HAM/TSP) and adult T-cell leukemia/lymphoma (ATL): systematic search and review. *J. Trop. Pediatr.* 64, 151–161.

- Oliver, N.W., Rowbottom, D.J., Sexton, P., Goldsmid, J.M., Byard, R., Tooth, M., Thomson, K.S., 1989. Chronic strongyloidiasis in Tasmanian veterans—clinical diagnosis by the use of a screening index. *Aust. N. Z. J. Med.* 19, 458–462.
- Olsen, A., van Lieshout, L., Marti, H., Polderman, T., Polman, K., Steinmann, P., Stothard, R., Thybo, S., Verweij, J.J., Magnussen, P., 2009. Strongyloidiasis—the most neglected of the neglected tropical diseases? *Trans. R. Soc. Trop. Med. Hyg.* 103, 967–972.
- Osei-Atweneboana, M.Y., Awadzi, K., Attah, S.K., Boakye, D.A., Gypapong, J.O., Prichard, R.K., 2011. Phenotypic evidence of emerging ivermectin resistance in *Onchocerca volvulus*. *PLoS Negl. Trop. Dis.* 5, e998.
- Osiro, S., Hamula, C., Glaser, A., Rana, M., Dunn, D., 2017. A case of *Strongyloides* hyperinfection syndrome in the setting of persistent eosinophilia but negative serology. *Diagn. Microbiol. Infect. Dis.* 88, 168–170.
- Oya, H., Mori, S., Tsuchihashi, H., Kurono, A., Mizoguchi, A., Kawabata, M., Arimura, K., Osame, M., 1998. A case of pleuritis caused by *Strongyloides* in a carrier of T-cell lymphoma virus type I (HTLV-I). *Nihon Kokyuki Gakkai zasshi* 36, 262–267.
- Page, W., 2011. Lessons from case histories, 6th National workshop on strongyloides. *Annals of the ACTM: An International Journal of Tropical and Travel Medicine*, 44–47. Cairns, Australia.
- Page, W., Judd, J.A., Bradbury, R.S., 2018. The unique life cycle of *Strongyloides stercoralis* and implications for public health action. *Trop. Med. Infect. Dis.* 3 (2), 53.
- Page, W., Speare, R., 2016. Chronic strongyloidiasis—don't look and you won't find. *Aust. Fam. Physician* 45, 40–44.
- Page, W.A., Dempsey, K., McCarthy, J.S., 2006. Utility of serological follow-up of chronic strongyloidiasis after anthelmintic chemotherapy. *Trans. R. Soc. Trop. Med. Hyg.* 100, 1056–1062.
- Paltridge, M., Smith, S., Traves, A., McDermott, R., Fang, X., Blake, C., Milligan, B., D'Addona, A., Hanson, J., 2020. Rapid progress toward elimination of strongyloidiasis in North Queensland, tropical Australia, 2000–2018. *Am. J. Trop. Med. Hyg.* 102, 339–345.
- Paltridge, M., Traves, A., de Costa, C., McDermott, R., 2019. Low prevalence of strongyloidiasis in Far North Queensland pregnant women. *Aust. J. Rural Health* 27, 438–439.
- Pasquier, A., Alais, S., Roux, L., Thoulouze, M.I., Alvarez, K., Journé, C., Dutartre, H., Mahieux, R., 2018. How to control HTLV-1-associated diseases: preventing de novo cellular infection using antiviral therapy. *Front. Microbiol.* 9, 278.
- Patel, J., Gupta, D., Rath, C., Parikh, P., Ingle, M., Sawant, P., 2015. Uncommon presentation of Strongyloidiasis: chronic malabsorption, multiple small bowel strictures and appendicitis in HTLV-1 positive patient. *Trop. Gastroenterol.* 36, 212–215.
- Patey, O., Bouhali, R., Breuil, J., Chapuis, L., Courillon-Mallet, A., Lafaix, C., 1990. Arthritis associated with *Strongyloides stercoralis*. *Scand. J. Infect. Dis.* 22, 233–236.
- Patey, O., Gessain, A., Breuil, J., Courillon-Mallet, A., Daniel, M.T., Miclea, J.M., Roucayrol, A.M., Sigaux, F., Lafaix, C., 1992. Seven years of recurrent severe strongyloidiasis in an HTLV-I-infected man who developed adult T-cell leukaemia. *AIDS (London, England)* 6, 575–579.
- Pattison, D.A., Speare, R., 2008. Strongyloidiasis in personnel of the regional assistance mission to Solomon Islands (RAMSI). *Med. J. Aust.* 189, 203–206.
- Patton, J.B., Bonne-Année, S., Deckman, J., Hess, J.A., Torigian, A., Nolan, T.J., Wang, Z., Kliever, S.A., Durham, A.C., Lee, J.J., Eberhard, M.L., Mangelsdorf, D.J., Lok, J.B., Abraham, D., 2018. Methylprednisolone acetate induces, and Δ^7 -dafachronic acid suppresses, *Strongyloides stercoralis* hyperinfection in NSG mice. *Proc. Natl. Acad. Sci. U. S. A.* 115, 204–209.

- Paxton, G.A., Sangster, K.J., Maxwell, E.L., McBride, C.R., Drewe, R.H., 2012. Post-arrival health screening in Karen refugees in Australia. *PLoS One* 7, e38194.
- Percher, F., Jeannin, P., Martin-Latil, S., Gessain, A., Afonso, P.V., Vidy-Roche, A., Ceccaldi, P.E., 2016. Mother-to-child transmission of HTLV-1 epidemiological aspects, mechanisms and determinants of mother-to-child transmission. *Viruses* 8 (2), 40.
- Phelps, K.R., Ginsberg, S.S., Cunningham, A.W., Tschachler, E., Dosik, H., 1991. Case report: adult T-cell leukemia/lymphoma associated with recurrent *Strongyloides* hyperinfection. *Am. J. Med. Sci.* 302, 224–228.
- Pilotte, N., Papaikovou, M., Grant, J.R., Bierwert, L.A., Llewellyn, S., McCarthy, J.S., Williams, S.A., 2016. Improved PCR-based detection of soil transmitted helminth infections using a next-generation sequencing approach to assay design. *PLoS Negl. Trop. Dis.* 10, e0004578.
- Plumelle, Y., Edouard, A., 1996. *Strongyloides stercoralis* in T-cell leukemia/lymphoma in adults and acquired immunodeficiency syndrome. *Rev. Med. Interne* 17, 125–129.
- Plumelle, Y., Gonin, C., Edouard, A., Bucher, B.J., Thomas, L., Brebion, A., Panelatti, G., 1997. Effect of *Strongyloides stercoralis* infection and eosinophilia on age at onset and prognosis of adult T-cell leukemia. *Am. J. Clin. Pathol.* 107, 81–87.
- Plumelle, Y., Pascaline, N., Nguyen, D., Panelatti, G., Jouannelle, A., Jouault, H., Imbert, M., 1993. Adult T-cell leukemia-lymphoma: a clinico-pathologic study of twenty-six patients from Martinique. *Hematol. Pathol.* 7, 251–262.
- Porto, A.F., Neva, F.A., Bittencourt, H., Lisboa, W., Thompson, R., Alcantara, L., Carvalho, E.M., 2001a. HTLV-1 decreases Th2 type of immune response in patients with strongyloidiasis. *Parasite Immunol.* 23, 503–507.
- Porto, A.F., Oliveira Filho, J., Neva, F.A., Orge, G., Alcantara, L., Gam, A., Carvalho, E.M., 2001b. Influence of human T-cell lymphocytotropic virus type 1 infection on serologic and skin tests for strongyloidiasis. *Am. J. Trop. Med. Hyg.* 65, 610–613.
- Porto, A.F., Santos, S.B., Alcantara, L., Guerreiro, J.B., Passos, J., Gonzalez, T., Neva, F., Gonzalez, D., Ho, J.L., Carvalho, E.M., 2004. HTLV-1 modifies the clinical and immunological response to schistosomiasis. *Clin. Exp. Immunol.* 137, 424–429.
- Porto, A.F., Santos, S.B., Muniz, A.L., Basilio, V., Rodrigues Jr., W., Neva, F.A., Dutra, W.O., Gollob, K.J., Jacobson, S., Carvalho, E.M., 2005a. Helminthic infection down-regulates type 1 immune responses in human T cell lymphotropic virus type 1 (HTLV-1) carriers and is more prevalent in HTLV-1 carriers than in patients with HTLV-1-associated myelopathy/tropical spastic paraparesis. *J Infect Dis* 191, 612–618.
- Porto, M.A., Alcantara, L.M., Leal, M., Castro, N., Carvalho, E.M., 2005b. Atypical clinical presentation of strongyloidiasis in a patient co-infected with human T cell lymphotropic virus type I. *Am. J. Trop. Med. Hyg.* 72, 124–125.
- Potter, A., Stephens, D., De Keulenaer, B., 2003. *Strongyloides* hyperinfection: a case for awareness. *Ann. Trop. Med. Parasitol.* 97, 855–860.
- Primo, J., Siqueira, I., Nascimento, M.C., Oliveira, M.F., Farre, L., Carvalho, E.M., Bittencourt, A.L., 2009. High HTLV-1 proviral load, a marker for HTLV-1 associated myelopathy/tropical spastic paraparesis, is also detected in patients with infective dermatitis associated with HTLV-1. *Braz. J. Med. Biol. Res.* 42, 761–764.
- Prociv, P., Adkins, J., 1987. Hyperinfection with *Strongyloides*. *Med. J. Aust.* 147, 363–364.
- Prociv, P., Luke, R., 1993. Observations on strongyloidiasis in Queensland aboriginal communities. *Med. J. Aust.* 158, 160–163.
- Queensland Department of Health, 1965–1966. Annual reports of the health and medical services of the state of Queensland. Queensland Government Printer, Brisbane.
- Rahim, S., Drabu, Y., Jarvis, K., Melville, D., 2005. Strongyloidiasis: a mistaken diagnosis and a fatal outcome in a patient with diarrhoea. *Trans. R. Soc. Trop. Med. Hyg.* 99, 215–217.

- Rahmanian, H., MacFarlane, A.C., Rowland, K.E., Einsiedel, L.J., Neuhaus, S.J., 2015. Seroprevalence of *Strongyloides stercoralis* in a South Australian Vietnam veteran cohort. *Aust. N. Z. J. Public Health* 39, 331–335.
- Rajababendaran, N., Burns, R., Mollison, L.C., Blessing, W., Kirubakaran, M.G., Lindschau, P., 1993. Tropical spastic paraparesis in an aborigine. *Med. J. Aust.* 159, 28–29.
- REM, 2020. Rem Indústria e Comércio LTDA.
- Requena-Mendez, A., Chiodini, P., Bisoffi, Z., Buonfrate, D., Gotuzzo, E., Munoz, J., 2013. The laboratory diagnosis and follow up of strongyloidiasis: a systematic review. *PLoS Negl. Trop. Dis.* 7, e2002.
- Reynoldson, J.A., Behnke, J.M., Pallant, L.J., Macnish, M.G., Gilbert, F., Giles, S., Spargo, R.J., Thompson, R.C., 1997. Failure of pyrantel in treatment of human hookworm infections (*Ancylostoma duodenale*) in the Kimberley region of north west Australia. *Acta Trop.* 68, 301–312.
- Ribier, G., Schroder, S., Ramialison, C., 1999. Why to look for vermin? *Rev. Med. Intern.* 20 (Suppl. 2), 277s–278s.
- Rice, J.E., Skull, S.A., Pearce, C., Mulholland, N., Davie, G., Carapetis, J.R., 2003. Screening for intestinal parasites in recently arrived children from East Africa. *J. Paediatr. Child Health* 39, 456–459.
- Richter, J., Schwarz, U., Duwe, S., Ellerbrok, H., Poggensee, G., Pauli, G., 2005. Recurrent strongyloidiasis as an indicator of HTLV-1 infection. *Deutsche Medizinische Wochenschrift* (1946) 130, 1007–1010.
- Riedel, D.J., Roddy, K.M., Sajadi, M.M., 2008. Abdominal pain and bacterial meningitis in a previously healthy young adult. *Clin. Infect. Dis.* 46 (1458), 1479–1480.
- Rio, B., Louvet, C., Gessain, A., Dormont, D., Gisselbrecht, C., Martoia, R., Auzanneau, G., Miclea, J.M., Baumelou, E., Dombret, H., et al., 1990. Adult T-cell leukemia and non-malignant adenopathies associated with HTLV I virus. Apropos of 17 patients born in the Caribbean region and Africa. *Presse Med. (Paris, France: 1983)* 19, 746–751.
- Robertson, G., Lade, C., Norton, R., Bradbury, R.S., 2014. The burden of helminth disease in Queensland, 2003–2013. In: Australian Society for Microbiology Annual Scientific Meeting 2014, Melbourne.
- Robertson, G.J., Koehler, A.V., Gasser, R.B., Watts, M., Norton, R., Bradbury, R.S., 2017. Application of PCR-based tools to explore *Strongyloides* infection in people in parts of northern Australia. *Trop. Med. Infect. Dis.* 2.
- Robinson, R.D., Lindo, J.F., Neva, F.A., Gam, A.A., Vogel, P., Terry, S.I., Cooper, E.S., 1994. Immunoepidemiologic studies of *Strongyloides stercoralis* and human T lymphotropic virus type I infections in Jamaica. *J. Infect. Dis.* 169, 692–696.
- Rocha, P.N., Rehem, A.P., Santana, J.F., Castro, N., Muniz, A.L., Salgado, K., Rocha, H., Carvalho, E.M., 2007. The cause of urinary symptoms among human T lymphotropic virus type I (HTLV-I) infected patients: a cross sectional study. *BMC Infect. Dis.* 7, 15.
- Rodriguez, E.A., Abraham, T., Williams, F.K., 2015. Severe strongyloidiasis with negative serology after corticosteroid treatment. *Am. J. Case Rep.* 16, 95–98.
- Sainte-Foie, S., Ast-Ravallec, G., 1991. Acute lymphocytic meningitis in a patient with *Anguillula* infestation and HTLV-1 virus infection. *Presse Med. (Paris, France: 1983)* 20, 1343.
- Saito, A., Aragaki, T., Kinjou, F., 1988. *Strongyloides* infection and bacterial meningitis in immunocompromised host, especially anti-HTLV-1 antibody positive patients. *Kansenshogaku zasshi* 62 (Suppl), 71–72.
- Salles, F., Bacellar, A., Amorim, M., Orge, G., Sundberg, M., Lima, M., Santos, S., Porto, A., Carvalho, E., 2013. Treatment of strongyloidiasis in HTLV-1 and *Strongyloides stercoralis* coinfecting patients is associated with increased TNF α and decreased soluble IL2 receptor levels. *Trans. R. Soc. Med. Hyg.* 107, 526–529.

- Salvador, F., Sulleiro, E., Piron, M., Sanchez-Montalva, A., Saulea, S., Molina, I., 2017. Seroprevalence of *Strongyloides stercoralis* infection among HTLV-I infected blood donors in Barcelona, Spain: a cross-sectional study. *Acta Trop.* 176, 412–414.
- Sampson, I., Smith, D.W., MacKenzie, B., 2003. Serological diagnosis of *Strongyloides stercoralis* infection. In: Second National Workshop on Strongyloidiasis, Brisbane.
- Sampson, I.A., Grove, D.I., 1987. Strongyloidiasis is endemic in another Australian population group: Indochinese immigrants. *Med. J. Aust.* 146, 580–582.
- Sandground, J.H., 1925. Speciation and specificity in the nematode genus *Strongyloides*. *J. Parasitol.* 12, 59–80.
- Sane, M., M'Baye, P.S., Morel, H., Michel, P., Talarmin, F., 1994. Recurrent anguilluliasis in a Senegalese infected with human T leukemia virus 1 (HTLV1). *Med. Trop.* 54, 375.
- Santos, S.B., Porto, A.F., Muniz, A.L., Jesus, A.R., Carvalho, E.M., 2004. Clinical and immunological consequences of human T cell leukemia virus type-I and *Schistosoma mansoni* co-infection. *Mem. Inst. Oswaldo Cruz* 99, 121–126.
- Sasaki, Y., Taniguchi, T., Kinjo, M., McGill, R.L., McGill, A.T., Tsuha, S., Shiiki, S., 2013. Meningitis associated with strongyloidiasis in an area endemic for strongyloidiasis and human T-lymphotropic virus-1: a single-center experience in Japan between 1990 and 2010. *Infection* 41, 1189–1193.
- Sato, Y., Shiroma, Y., 1989. Concurrent infections with *Strongyloides* and T-cell leukemia virus and their possible effect on immune responses of host. *Clin. Immunol. Immunopathol.* 52, 214–224.
- Sato, Y., Shiroma, Y., Kiyuna, S., Toma, H., Kobayashi, J., 1994. Reduced efficacy of chemotherapy might accumulate concurrent HTLV-1 infection among strongyloidiasis patients in Okinawa, Japan. *Trans. R. Soc. Trop. Med. Hyg.* 88, 59.
- Satoh, M., Futami, A., Takahira, K., Kodaira, M., Tanaka, T., Kuriki, K., Hori, E., 2003. Severe strongyloidiasis complicated by meningitis and hydrocephalus in an HTLV-1 carrier with increased proviral load. *J. Infect. Chemother.* 9, 355–357.
- Satoh, M., Toma, H., Sato, Y., Takara, M., Shiroma, Y., Kiyuna, S., Hirayama, K., 2002. Reduced efficacy of treatment of strongyloidiasis in HTLV-I carriers related to enhanced expression of IFN-gamma and TGF-beta1. *Clin. Exp. Immunol.* 127, 354–359.
- Satoh, M., Tsukidate, S., Fujita, K., Yamamoto, K., 1991. Strongyloidiasis influences the elevation of adult T-cell leukemia-associated antigen antibody titer. *Int. Arch. Allergy Appl. Immunol.* 96, 95–96.
- Schad, G.A., 1989. *Morphology and Life History of Strongyloides stercoralis*. Taylor and Francis, London.
- Schad, G.A., Thompson, F., Talham, G., Holt, D., Nolan, T.J., Ashton, F.T., Lange, A.M., Bhopale, V.M., 1997. Barren female *Strongyloides stercoralis* from occult chronic infections are rejuvenated by transfer to parasite-naïve recipient hosts and give rise to an auto-infective burst. *J. Parasitol.* 83, 785–791.
- Schär, F., Trostorf, U., Giardina, F., Khieu, V., Muth, S., Marti, H., Vounatsou, P., Odermatt, P., 2013. *Strongyloides stercoralis*: global distribution and risk factors. *PLoS Negl. Trop. Dis.* 7, e2288.
- Schein, F., Fouillet, L., Lutz, M.F., Dagueuet, E., Botelho-Nevers, E., Cornillon, J., 2018. Recurrent *Enterococcus faecalis* meningitis in a patient presenting with *Strongyloides* hyperinfection syndrome during HTLV-1-induced T-cell lymphoma. *Med. Mal. Infect.* 48, 428–430.
- Sheremata, W.A., Harrington Jr., W.J., Bradshaw, P.A., Fong, S.K., Raffanti, S.P., Berger, J.R., Snodgrass, S., Resnick, L., Poiesz, B.J., 1993. Association of '(tropical) ataxic neuropathy' with HTLV-II. *Virus Res.* 29, 71–77.
- Shidrawi, R.G., Shousha, S., Westaby, D., 1994. Systemic strongyloidiasis in an HTLV-1 positive male presenting as chronic pancreatitis with a pancreatico-biliary stricture. *Eur. J. Gastroenterol. Hepatol.* 6, 1059–1062.

- Shidrawi, R.G., Westaby, D., 1994. Strongyloidiasis. *Gut* 35, 1772.
- Shield, J., Aland, K., Kearns, T., Gongdjalk, G., Holt, D., Currie, B., Prociv, P., 2015. Intestinal parasites of children and adults in a remote Aboriginal community of the Northern Territory, Australia, 1994–1996. *Western Pac. Surveill. Response J.* 6, 44–51.
- Shield, J.M., Page, W., 2008. Effective diagnostic tests and anthelmintic treatment for *Strongyloides stercoralis* make community control feasible. *Papua New Guinea Med. J.* 51, 105–119.
- Shoop, W.L., Michael, B.F., Eary, C.H., Haines, H.W., 2002. Transmammary transmission of *Strongyloides stercoralis* in dogs. *J. Parasitol.* 88, 536–539.
- Smith, J.D., Goette, D.K., Odom, R.B., 1976. Larva currens. Cutaneous strongyloidiasis. *Arch. Dermatol.* 112, 1161–1163.
- Smith, S., Russell, D., Horne, P., Hanson, J., 2019. HTLV-1 is rare in Far North Queensland despite a significant burden of classically associated diseases. *Pathology* 51, 91–94.
- Soulsby, H.M., Hewagama, S., Brady, S., 2012. Case series of four patients with *Strongyloides* after occupational exposure. *Med. J. Aust.* 196, 444.
- Speare, R., 1989. Identification of Species of *Strongyloides*. Taylor and Francis, London, New York.
- Speare, R., Durrheim, D.N., 2004. Strongyloides serology—useful for diagnosis and management of strongyloidiasis in rural indigenous populations, but important gaps in knowledge remain. *Rural Remote Health* 4, 264.
- Stauffer, W.M., Alpern, J.D., Walker, P.F., 2020. COVID-19 and dexamethasone: a potential strategy to avoid steroid-related *Strongyloides* hyperinfection. *JAMA* 324 (7), 623–624.
- Steinfert, D.P., Brady, S., Weisinger, H.S., Einsiedel, L., 2008. Bronchiectasis in Central Australia: a young face to an old disease. *Respir. Med.* 102, 574–578.
- Steinmann, P., Zhou, X.N., Du, Z.W., Jiang, J.Y., Wang, L.B., Wang, X.Z., Li, L.H., Marti, H., Utzinger, J., 2007. Occurrence of *Strongyloides stercoralis* in Yunnan Province, China, and comparison of diagnostic methods. *PLoS Negl. Trop. Dis.* 1, e75.
- Strkolcova, G., Goldova, M., Bockova, E., Mojzisova, J., 2017. The roundworm *Strongyloides stercoralis* in children, dogs, and soil inside and outside a segregated settlement in Eastern Slovakia: frequent but hardly detectable parasite. *Parasitol. Res.* 116, 891–900.
- Styles, C.E., Hoad, V.C., Seed, C.R., 2018. Estimation of human T-lymphotropic virus incidence in blood donors from observed prevalence. *Vox Sang.* 113, 814–815.
- Styles, C.E., Seed, C.R., Hoad, V.C., Gaudieri, S., Keller, A.J., 2017. Reconsideration of blood donation testing strategy for human T-cell lymphotropic virus in Australia. *Vox Sang.* 112, 723–732.
- Sugiura, A., Fujimoto, M., Saida, Y., 2006. Enterococcal meningitis due to strongyloidiasis with HTLV-1 carrier. *Rinsho shinkeigaku* 46, 715–717.
- Sugiyama, H., Doi, H., Yamaguchi, K., Tsuji, Y., Miyamoto, T., Hino, S., 1986. Significance of postnatal mother-to-child transmission of human T-lymphotropic virus type-I on the development of adult T-cell leukemia/lymphoma. *J. Med. Virol.* 20, 253–260.
- Sultana, Y., Gilbert, G.L., Ahmed, B.N., Lee, R., 2012. Seroepidemiology of *Strongyloides stercoralis* in Dhaka, Bangladesh. *Parasitology* 139, 1513–1520.
- Sultana, Y., Jeoffreys, N., Watts, M.R., Gilbert, G.L., Lee, R., 2013. Real-time polymerase chain reaction for detection of *Strongyloides stercoralis* in stool. *Am. J. Trop. Med. Hyg.* 88, 1048–1051.
- Suputtamongkol, Y., Premasathian, N., Bhumimuang, K., Waywa, D., Nilnanuwong, S., Karuphong, E., Anekthananon, T., Wanachiwanawin, D., Silpasakorn, S., 2011. Efficacy and safety of single and double doses of ivermectin versus 7-day high dose albendazole for chronic strongyloidiasis. *PLoS Negl. Trop. Dis.* 5, e1044.
- Tanaka, T., Hirata, T., Parrott, G., Higashiarakawa, M., Kinjo, T., Kinjo, T., Hokama, A., Fujita, J., 2016. Relationship among *Strongyloides stercoralis* infection, human T-cell

- lymphotropic virus type 1 infection, and cancer: a 24-year cohort inpatient study in Okinawa, Japan. *Am. J. Trop. Med. Hyg.* 94, 365–370.
- Tanaka, T., Sekioka, T., Usui, M., Imashuku, S., 2015. Opportunistic infections in patients with HTLV-1 infection. *Case Rep Hematol* 2015, 943867.
- Taniguchi, A., Mochizuki, H., Yamashita, A., Shiomi, K., Asada, Y., Nakazato, M., 2017. Spinal cord anteroposterior atrophy in HAM/TSP: magnetic resonance imaging and neuropathological analyses. *J. Neurol. Sci.* 381, 135–140.
- Tariq, H., Kamal, M.U., Reddy, P., Bajantri, B., Niazi, M., Matela, A., Zeana, C., Ihimoyan, A., Dev, A., Chilimuri, S., 2017. Anemia, intractable vomiting, chronic diarrhea, and syndrome of inappropriate antidiuretic secretion: a diagnostic dilemma: disseminated strongyloidosis in a patient with newly diagnosed HTLV infection—case report and review of literature. *Medicine* 96, e9229.
- Teixeira, M.C., Pacheco, F.T., Souza, J.N., Silva, M.L., Ines, E.J., Soares, N.M., 2016. *Strongyloides stercoralis* infection in alcoholic patients. *Biomed. Res. Int.* 2016, 4872473.
- Terashima, A., Alvarez, H., Tello, R., Infante, R., Freedman, D.O., Gotuzzo, E., 2002. Treatment failure in intestinal strongyloidiasis: an indicator of HTLV-I infection. *Int. J. infect. Dis.* 6, 28–30.
- Thanchomnang, T., Intapan, P.M., Sanpool, O., Rodpai, R., Sadaow, L., Phosuk, I., Somboonpatarakun, C., Laymanivong, S., Tourtip, S., Maleewong, W., 2019. First molecular identification of *Strongyloides fuelleborni* in long-tailed macaques in Thailand and Lao People's Democratic Republic reveals considerable genetic diversity. *J. Helminthol.* 93, 608–615.
- Thanchomnang, T., Intapan, P.M., Sanpool, O., Rodpai, R., Tourtip, S., Yahom, S., Kullawat, J., Radomyos, P., Thammasiri, C., Maleewong, W., 2017. First molecular identification and genetic diversity of *Strongyloides stercoralis* and *Strongyloides fuelleborni* in human communities having contact with long-tailed macaques in Thailand. *Parasitol. Res.* 116, 1917–1923.
- Thorstensson, R., Albert, J., Andersson, S., 2002. Strategies for diagnosis of HTLV-I and -II. *Transfusion* 42, 780–791.
- Thulin Hedberg, S., Eriksson, L., Demontis, M.A., Molling, P., Sundqvist, M., Taylor, G., Malm, K., Andersson, S., 2018. Droplet digital PCR for absolute quantification of proviral load of human T-cell lymphotropic virus (HTLV) types 1 and 2. *J. Virol. Methods* 260, 70–74.
- Toma, H., Sato, Y., Shiroma, Y., Kobayashi, J., Shimabukuro, I., Takara, M., 2000. Comparative studies on the efficacy of three anthelmintics on treatment of human strongyloidiasis in Okinawa, Japan. *Southeast Asian J. Trop. Med. Public Health* 31, 147–151.
- Troncoso Garcia, E., Munoz Medina, L., Callejas Rubio, J.L., Lopez Ruz, M.A., 2000. *Klebsiella pneumoniae* meningitis, *Strongyloides stercoralis* infection and HTLV-1. *Med. Clin.* 115, 158.
- Trope, B.M., Lenzi, M.E., 2009. Infective dermatitis. *Clin. Dermatol.* 27, 281–284.
- Turner, J.D., Faulkner, H., Kamgno, J., Cormont, F., Van Snick, J., Else, K.J., Grencis, R.K., Behnke, J.M., Boussinesq, M., Bradley, J.E., 2003. Th2 cytokines are associated with reduced worm burdens in a human intestinal helminth infection. *J. Infect Dis* 188, 1768–1775.
- Udaka, M., Maehara, N., Tamaki, K., Fukuhara, H., Kaneshima, H., Nakamura, H., Irabu, Y., Shimoji, K., Kitsukawa, K., Shigeno, Y., et al., 1990. A case of *Pneumocystis carinii* pneumonia with hyperinfection of *Strongyloides stercoralis* complicated with smoldering adult T-cell leukemia. *Kansenshogaku zasshi* 64, 630–635.
- van Doorn, H.R., Koelwij, R., Hofwegen, H., Gilis, H., Westeyn, J.C.F.M., Wismans, P.J., Sarfati, C., Vervoort, T., van Gool, T., 2007. Use of enzyme-linked immunosorbent assay and dipstick assay for detection of *Strongyloides stercoralis* infection in humans. *J. Clin. Microbiol.* 45, 438–442.

- Van Rensburg, E.J., Lemmer, H.R., Joubert, J.J., 1995. Prevalence of viral infections in Mozambican refugees in Swaziland. *East Afr. Med. J.* 72, 588–590.
- Verdonck, K., Gonzalez, E., Van Dooren, S., Vandamme, A.M., Vanham, G., Gotuzzo, E., 2007. Human T-lymphotropic virus 1: recent knowledge about an ancient infection. *Lancet Infect. Dis.* 7, 266–281.
- Verweij, J.J., Canales, M., Polman, K., Ziem, J., Brienens, E.A.T., Polderman, A.M., van Lieshout, L., 2009. Molecular diagnosis of *Strongyloides stercoralis* in faecal samples using real-time PCR. *Trans. R. Soc. Trop. Med. Hyg.* 103, 342–346.
- Viana, G.M., Silva, M.A., Souza, V.L., Lopes, N.B., Silva, D.L., Nascimento Mdo, D., 2014. Interferon beta-1a treatment in HTLV-1-associated myelopathy/tropical spastic paraparesis: a case report. *Rev. Inst. Med. Trop. Sao Paulo* 56, 443–445.
- Viney, M.E., Ashford, R.W., Barnish, G., 1991. A taxonomic study of *Strongyloides* Grassi, 1879 (Nematoda) with special reference to *Strongyloides fuelleborni* von linstow, 1905 in man in Papua New Guinea and the description of a new subspecies. *Syst. Parasitol.* 18, 95–109.
- Viney, M.E., Lok, J.B., 2007. *Strongyloides* spp. ed, The *C. elegans* Research Community, WormBook, <http://www.wormbook.org>, WormBook.
- Visy, J.M., Vassel, P., Chaîne, P., Woimant, F., Dumas, J.L., Lhote, F., Mainguene, C., Haguénau, M., 1993. Meningoradiculitis disclosing T-lymphocyte leukemia in HTLV-1 infection. *Rev. Neurol.* 149, 428–431.
- von Kuster, L.C., Genta, R.M., 1988. Cutaneous manifestations of strongyloidiasis. *Arch. Dermatol.* 124, 1826–1830.
- Walker-Smith, J.A., McMillan, B., Middleton, A.W., Robertson, S., Hopcroft, A., 1969. Strongyloidiasis causing small-bowel obstruction in an aboriginal infant. *Med. J. Aust.* 2, 1263–1265.
- Wang, Y., Ma, Y., Xu, Y., Zhu, B., Guo, H., 2014. *Strongyloides stercoralis* disseminated infection in a patient misdiagnosed with chronic asthmatic bronchitis. *J. Microbiol. Immunol. Infect.* 88, 2786–2798.
- Watts, M.R., James, G., Sultana, Y., Ginn, A.N., Outhred, A.C., Kong, F., Verweij, J.J., Iredell, J.R., Chen, S.C., Lee, R., 2014. A loop-mediated isothermal amplification (LAMP) assay for *Strongyloides stercoralis* in stool that uses a visual detection method with SYTO-82 fluorescent dye. *Am. J. Trop. Med. Hyg.* 90, 306–311.
- Watts, M.R., Kim, R., Ahuja, V., Robertson, G.J., Sultana, Y., Wehrhahn, M.C., Bradbury, R.S., Gilbert, G.L., Lee, R., 2019. Comparison of loop-mediated isothermal amplification and real-time PCR assays for detection of *Strongyloides* larvae in different specimen matrices. *J. Clin. Microbiol.* 57.
- Weerakoon, K.G., Gordon, C.A., Williams, G.M., Cai, P., Gobert, G.N., Olveda, R.M., Ross, A.G., Olveda, D.U., McManus, D.P., 2018. Co-parasitism of intestinal protozoa and *Schistosoma japonicum* in a rural community in the Philippines. *Infect. Dis. Poverty* 7, 121.
- WHO, 2019a. Neglected Tropical Diseases.
- WHO, 2019b. Strongyloidiasis.
- Whyte, G.S., 1997. Is screening of Australian blood donors for HTLV-I necessary? *Med. J. Aust.* 166, 478–481.
- Wilson, A., Fearon, D., 2019. An unusual rash: *Strongyloides stercoralis* presenting as larva currens in a 12-year-old girl with Crohn's disease. *J. Paediatr. Child Health* 55, 364–366.
- Wulcan, J.M., Dennis, M.M., Ketzis, J.K., Bevelock, T.J., Verocai, G.G., 2019. *Strongyloides* spp. in cats: a review of the literature and the first report of zoonotic *Strongyloides stercoralis* in colonic epithelial nodular hyperplasia in cats. *Parasit. Vectors* 12, 349.
- Wylie, B., 1993. HTLV-I: is donor screening really necessary? *Med. J. Aust.* 159, 4–5.

- Wylie, B.R., Thomson, A.R., 1992. HTLV-I infection in selected populations in Australia and the western Pacific region. *Med. J. Aust.* 157, 286–287.
- Yamada, M., Matsuda, S., Nakazawa, M., Arizono, N., 1991. Species-specific differences in heterogonic development of serially transferred free-living generations of *Strongyloides planiceps* and *Strongyloides stercoralis*. *J. Parasitol.* 77, 592–594.
- Yiannakou, J., Croese, J., Ashdown, L.R., Prociv, P., 1990. Strongyloidiasis in North Queensland: re-emergence of a forgotten risk group? *Med. J. Aust.* 156, 24–27.
- Yokota, T., Yamada, M., Furukawa, T., Tsukagoshi, H., 1988. HTLV-I-associated meningo-itis. *J. Neurol.* 235, 129–130.
- Yong, M.K., Marshall, C.L., Eisen, D.P., 2007. Tropical pulmonary eosinophilia: a rare cause of cough in immigrants to Australia. *Med. J. Aust.* 187, 416–418.
- Zaha, O., Hirata, T., Kinjo, F., Saito, A., Fukuhara, H., 2002. Efficacy of ivermectin for chronic strongyloidiasis: two single doses given 2 weeks apart. *J. Infect. Chemother.* 8, 94–98.
- Zak, A., Siwinska, N., Slowikowska, M., Borowicz, H., Kubiak, K., Hildebrand, J., Popiolek, M., Niedzwiedz, A., 2017. Searching for ivermectin resistance in a Strongylidae population of horses stabled in Poland. *BMC Vet. Res.* 13, 210.
- Zammarchi, L., Montagnani, F., Tordini, G., Gotuzzo, E., Bisoffi, Z., Bartoloni, A., De Luca, A., 2015. Persistent strongyloidiasis complicated by recurrent meningitis in an HTLV seropositive Peruvian migrant resettled in Italy. *Am. J. Trop. Med. Hyg.* 92, 1257–1260.
- Zubrinich, C.M., Puy, R.M., O’Hehir, R.E., Hew, M., 2019. *Strongyloides* infection as a reversible cause of chronic urticaria. *Journal of Asthma and Allergy* 12, 67–69.