Pathology (December 2019) **51(7)**, pp. 737–741

MICROBIOLOGY

Declining soil transmitted helminth detections in an Australian tropical region

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Summary

Soil-transmitted helminths (STHs), are recognised neglected tropical diseases and have been endemic in patients in tropical Northern Australia. We reviewed the temporal trends in detections of STHs and *Hymenolepis nana* in faecal samples from Northern Territory (NT) Government Health facilities, representing patients with acute illnesses and comorbidities between 2008 and 2018. *Ascaris lumbricoides* is not detected in patients in the NT. The number of faecal samples examined yearly was relatively constant with a median of 4458 (range 4246–4933). Faecal samples from patients under the age of 5 years declined by 45% over the 11 years of the study. Detections of *Trichuris trichiura*, *Strongyloides* spp., and hookworm ova fell significantly by 89% ($p<0.001$), 71% ($p<0.001$), and 43% ($p<0.01$), respectively, over the 11 years. Detections of *H. nana* declined by 33% absolutely, but not significantly, when assessed relative to the reduction in faecal samples from patients under the age of 5 years. The marked reduction in STH numbers coincided with a 10-fold increase in NT dispensing of ivermectin, predominantly used for scabies control, in widely geographically spaced locations throughout the NT, over the 11 years of the study. Our data support previous findings of the beneficial collateral effects of ivermectin therapy. Ivermectin is not recognised as having anti-cestode activity, hence the continued presence of *H. nana* endemically in the NT, suggests declines in STHs are not related to other changes in health hardware or existing mass drug administration programs. The reduction in *T. trichiura* detections may not be explained by this association, as unlike *Strongyloides* spp., the anti-helminthic effect of ivermectin has been less marked.

Key words: Soil transmitted helminths; *Strongyloides spp*; *Hymenolepis nana*; Northern Territory; Australia.

Received 27 June, revised 28 August, accepted 3 September 2019
Available online 18 October 2019

INTRODUCTION

The neglected tropical diseases caused by the soil transmitted helminths (STHs) *Strongyloides* spp., hookworm, and *Trichuris trichiura* are present endemically in patients from the Northern Territory (NT) of Australia, a large but sparsely populated tropical area, covering 1.4 million square kilometres (17% of Australia's landmass). Worldwide three species of *Strongyloides* are known to parasitise humans, *Strongyloides stercoralis*, *S. fuelleborni* and *S. fuelleborni kellyi*, which can require specialist techniques to differentiate. In tropical Australian Aboriginal and Torres Strait Islander communities, infection with *S. stercoralis* is common.[1] Previous laboratory studies[2–5] have shown these STHs predominantly occur in indigenous patients, and are spread widely over the entire geography of the NT. The NT also has an endemic cestode infection, *Hymenolepis nana*, predominantly infecting children under 5 years of age,[6] unlike the STHs which are found more widely across patient age groups.[2–5]

Temporal trends have shown a gradual decline in STH numbers over time, and now the more severe STH associated syndromes, such as swollen belly syndrome and anaemia,[7,8] caused by *Strongyloides* spp. infections and hookworm, respectively, are very rare. Reductions are attributed partially to a longstanding albendazole mass drug administration program in target groups.[2] In particular, hookworm (*Ancylostoma duodenale*) has been targeted by an Indigenous community children's deworming program (CCDP) in the NT since 1995, which administers single dose albendazole twice a year to children aged 6 months to 16 years.[2] The albendazole given as part of the CCDP has been associated with decreases in the detection of *Strongyloides* spp. and *T. trichiura*[5] in the same population. There has also been a decrease in paediatric hospitalisation of children, as introduction of rotavirus vaccine and widespread use of oral rehydration solutions have reduced paediatric gastroenteritis admissions to health services,[9] hence potentially less inpatient screening of paediatric patients is occurring.

A more recent development in mass drug administration in Australia has been the targeted use of ivermectin in communities leading to a documented reduction in *Strongyloides* spp. sero-prevalence.[10,11] Therapeutic use of ivermectin for scabies control, or as part of mass drug administration programs, has also been associated with a collateral reduction in STH prevalence.[12] Ivermectin is not active against the cestode dwarf tapeworm, *H. nana*, and is less active against *T. trichiura*.[13]

Our aim was to describe the temporal trend in NT STH detection, and the cestode, *H. nana*, in faecal samples assayed in NT Government health facilities over a period of 11 years, comparing detection trends to the relative dispensing rates of ivermectin during this period.

Print ISSN 0031-3025/Online ISSN 1465-3931
DOI: https://doi.org/10.1016/j.pathol.2019.09.002

MATERIALS AND METHODS

We conducted a retrospective observational review of microbiologically detected *Strongyloides* spp. larvae, hookworm ova, *T. trichiura* ova, and *H. nana* ova in faecal samples collected at NT Government health facilities between 2008 and 2018, inclusive. All faecal samples were included, but only one of each parasite/episode was recorded for similar parasites detected within 6 months of the index specimen (i.e., duplicate parasite detections within 6 months were not recounted). Ethical approval for the study was obtained from the regional ethics committee (HREC 2018–3256). Cases were identified from the NT Government pathology laboratory information system, Labtrak (Intersystems, Australia), which covers all NT Government health facilities, including six hospitals, two correctional centres and over 50 remote clinics. The episodes were linked to NT government electronic databases via medical record number to obtain data on geographic residence of individuals (Central Australia or Top End). Parasite identification was performed by faecal specimen examination using wet mount microscopy followed by a concentration method[14]; agar culture and Harada culture were not performed routinely. Local standard reporting procedures were followed. Quantitative assessment of parasites was not carried out. Ivermectin dispensing data were obtained from NT Department of health pharmacy, from the NT Primary Care Information System (PCIS) database.

Statistical analysis

Data were collected in a Microsoft Excel 2017 (Microsoft Corporation, USA) database and Chi square analysed using the Real Statistics Using Excel plug in (www.real-statistics.com). Population data from the NT were obtained from Australian Bureau of Statistics data.[15] The cut-off age of 5 years for *H. nana* was chosen based on previous studies of STH in the NT.[6]

RESULTS

Between 2008 and 2018, 49,679 faecal samples were examined microscopically for ova, cysts and parasites (OCP) across NT Government health facilities, which are separated into two distinct geographic regions, Top End and Central. The population of the NT is ~250,000, with five-fold more individuals residing in the Top End, compared to the Central region. The number of annual faecal samples tested remained relatively constant throughout this time period, with a median of 4458 samples/year (range 4246–4933). Faecal samples from paediatric patients under the age of 5 years represented 42.1% of all samples. However, there was a relatively steady decrease in faecal samples from paediatric patients under the age of 5 years of age, over the 11 years of the study, in both absolute number and percentage terms (Table 1) from both Central Australia and Top End. Faeces samples arising from Central Australia represented 43% of total faecal samples in this study.

There were marked geographic differences in detection of STHs over the 11 years with only one patient with hookworm ova and one patient with *T. trichiura* ova detected from Central Australia specimens, compared to 43 and 203 detections from the Top End, respectively.

Of the individual STHs, *Strongyloides* spp. larvae were detected in 240 (0.48%) of all faecal samples, numerically predominantly from Top End collected samples, but given the population differences, a relatively even distribution of detections. Detections as percentage of all yearly faecal samples decreased by 71% over the 11 years. *Trichuris trichiura* numbers declined by 89% over the 11 years, and hookworm detections a smaller 43%, but much lower hookworm numbers were present in total (Table 1). Hookworm and *T. trichiura* detections are now very low (Fig. 1), almost totally absent from Central Australia, and declining significantly in the Top End, where they were previously common.

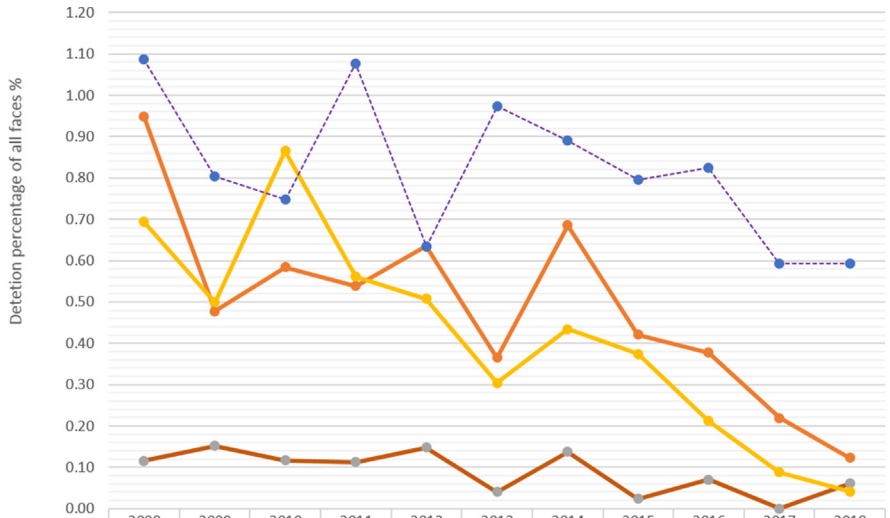
The cestode, *H. nana* was present geographically across the NT. *Hymenolepis nana* detections as percentage of total number of faecal samples (Fig. 1) reduced by 33%, in correlation with the reduction in absolute and percentage numbers of faecal samples from the under 5 age group. This decrease in faecal numbers represents a 45% reduction in faecal numbers from this age group, which is the group historically with the greatest burden of *H. nana* infection. However, *H. nana* detections as a percentage of faecal samples from patients under 5 years of age, showed no numeric or percentage decline.

Ivermectin dispensing as recorded by PCIS has increased 10-fold (Fig. 2) over the past 11 years. This figure excludes hospital use, research use, and public health use, so is an underestimate of total use in the NT, but the figure does reflect the relative increasing use of this medication. It is usually recommended for adults, but not very young children under 15kg in weight. The number of centres where ivermectin was dispensed (Fig. 2) increased over 3-fold, and represented widely geographically spaced urban and remote locations across the NT.

Table 1 Northern Territory public laboratory detection of STHs and *Hymenolepis nana* by faecal sample numbers, and age of patient <5

Year	Faecal specimens examined	No. faeces from patients <5 years of age (% of total)	*Strongyloides* spp.			Hookworm ova[a]	*Trichuris trichiura* ova[b]	*Hymenolepis nana*		
			Central	Top End	Total	Total	Total	Central	Top End	Total
2008	4327	2278 (52.7)	16	25	41	5	30	24	23	47
2009	4605	2603 (56.5)	2	20	22	7	23	15	22	37
2010	4278	2327 (54.4)	0	25	25	5	37	17	15	32
2011	4458	2041 (45.8)	4	20	24	5	25	24	24	48
2012	4725	2007 (42.5)	6	24	30	7	24	14	16	30
2013	4933	2257 (45.8)	1	17	18	2	15	24	24	48
2014	4379	1660 (37.9)	4	26	30	6	19	14	25	39
2015	4279	1520 (35.5)	2	16	18	1	16	16	18	34
2016	4246	1325 (31.2)	0	16	16	3	9	23	12	35
2017	4562	1472 (32.3)	3	7	10	0	4	14	13	27
2018	4887	1423 (29.1)	0	6	6	3	2	22	7	29
Total	49679	20913 (42.1)	38	202	240	44	204	207	199	406

[a] One hookworm ova only detected from Central Australia in 2009, all others from Top End patients.
[b] One *T. trichiura* ova only detected in Central Australia in 2008, all others from Top End patients.



	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Strongyloides spp (% of all faeces)	0.95	0.48	0.58	0.54	0.63	0.36	0.69	0.42	0.38	0.22	0.12
Hookworm (% of all faeces)	0.12	0.15	0.12	0.11	0.15	0.04	0.14	0.02	0.07	0.00	0.06
T. trichiura (% of all faeces)	0.69	0.50	0.86	0.56	0.51	0.30	0.43	0.37	0.21	0.09	0.04
H. nana (% of all faeces)	1.09	0.80	0.75	1.08	0.63	0.97	0.89	0.79	0.82	0.59	0.59

Fig. 1 Trends in detection of soil transmitted helminths 2008–2018 in the Northern Territory.

DISCUSSION

Our study reveals a recent rapid fall in STH detections both numerically, and as a percentage of faecal samples examined in NT Government health facilities. Detections of hookworm and *T. trichiura* are now very rare in public laboratories in Central Australia, possibly related to unfavourable soil conditions. The smaller 33% numerical decrease in *H. nana* detections can be predominantly attributed to the 45% reduction in faecal samples from children under 5 years of age during the 11 year study period, but this is unlikely to explain the larger reductions in *Strongyloides* spp. and *T. trichiura* numbers. Previous studies[5] have shown a biphasic distribution of *Strongyloides* spp. detection in public labs in the NT, with only 42% of detections occurring in patients under 5 years of age. Similarly, with *T. trichiura,* only 44% of detections were in patients under 5.[3] So for both of these STHs there were previously significant numbers of infections detected in adult patients, suggesting the declines are real and not related to absolute faecal numbers examined or other methodological changes in sampling. There was a comparatively smaller decrease in hookworm detections, but the numbers were low to start with, and the trend is still downwards, and again adult infections are well documented in this population.[2]

The reduction in *Strongyloides* numbers is associated with increased ivermectin use, as described by other authors. The study by Kearns *et al.*[10] based in the NT does provide local evidence of ivermectin efficacy against *Strongyloides* spp. sero-prevalence, in particular. Other possible drivers of STH decrease, such as alterations to the long standing albendazole mass drug administration programs or improvements in health hardware, such as sanitation and housing overcrowding have not changed or markedly improved during these 11 years to account for the reductions in detections. Ivermectin is not always used in young children and The Central Australian Rural Practitioners Association (CARPA)[16] currently recommends for *S. stercoralis* therapy: albendazole daily for 3 days (children ≤5 years of age), or ivermectin for children >5 and adults. The optimal ivermectin regimen for treatment of strongyloidiasis is uncertain; thus far, no regimen is clearly superior. Standard dosing of ivermectin consists of two 200 µg/kg doses of ivermectin administered on two consecutive days or administered 2 weeks apart, however we believe most prescribing was associated with scabies control programs.

Ivermectin, even in combination with albendazole, is less efficacious against *T. trichiura*[13] than against strongyloides and hookworm, raising the possibility that a different factor is responsible for the drop in STH detections. *Trichuris trichiura* numbers fell by 89%, so a combination of other factors may be involved.

Hymenolepis nana is the most frequently identified cestode (tapeworm) in NT Government health-care facilities. It remains endemic throughout the NT, predominantly infecting Indigenous children less than 5 years of age.[6] As the infection is associated with less morbidity than the STHs it has not been a primary or secondary target of local mass drug administration programs. For this reason, it remains a biological indicator organism of challenges in sanitation and health hardware for communities with infections. While there was a decline in numbers, this can be fully attributed to the decline in faecal specimen numbers from patients less than 5 years of age examined.

Our retrospective study has several limitations and several potential biases that require consideration when interpreting these data. This was not a formal prevalence study, as systematic sampling from individual communities was not undertaken, so the actual rates are almost certainly higher than the laboratory microscopically diagnosed rates found in our study population. The study population mainly reflected inpatients of NT Government health facilities, reflecting a selection bias towards patients with acute illness and comorbid conditions. Bias may have been introduced in

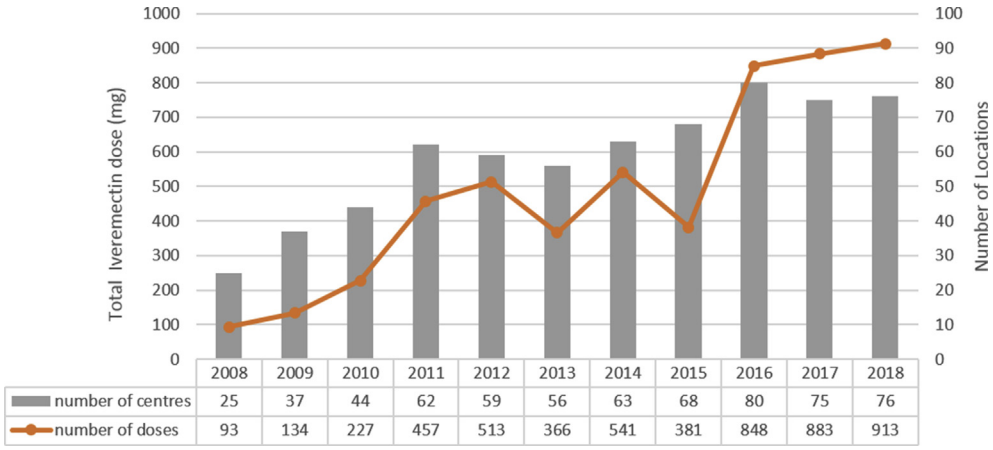


Fig. 2 Ivermectin doses dispensed and locations by year in the Northern Territory.

regards to Indigenous status (as Indigenous patients are over-represented amongst admissions to NT healthcare facilities). Reduced recovery of parasites is a possible issue, due to delays incurred by transport of specimens to the laboratory from remote locations. Ova tend to survive transport delays, though hookworm ova sometimes hatch, and the larvae must be distinguished morphologically from *Strongyloides* spp.

The second limitation is the detection of STHs by microscopy alone, which is known to be insensitive. This study used the definitive microscopic method of STH ova and larvae detection as the diagnostic tool throughout the 11 years of the study. The gold standard for the diagnosis of STH detection remains serial stool examination.[14] However, traditional individual stool examinations are insensitive, and require up to seven stool exams to reach a sensitivity of 100%. Intermittent shedding of *Strongyloides* larvae reduces sensitivity. Specialised stool exams include Harada-Mori filter paper culture, quantitative acetate concentration technique, and nutrient agar plate cultures [14] may assist. Detection by nucleic acid amplification of STH DNA is in development, but has not as yet been demonstrated to be superior to traditional methods for *S. stercoralis* infection,[17] and is not yet widely available in all rural and remote microbiology laboratories.

Thirdly, our data on ivermectin use are illustrative only of the relative increase in dispensing, and do not represent total NT use, as they do not include public hospital use, mass drug administration trials, and off label use. However, they do illustrate a relative 10-fold increase in dose dispensing over the 11 years of the study, and the widespread use as indicted by the number of sites of dispensation.

The temporal trend over the 11 years of this study reveals declining rates of STH detection in NT Government public health facilities, in particular *Strongyloides* spp., *T. trichiura*, and hookworm. The associated increasing human use of ivermectin in the NT suggests a collateral benefit of scabies control programs. *Hymenolepis nana* remains endemic, and numbers are relatively constant per paediatric faecal specimen examined; we note the inactivity of ivermectin against the cestode, and the infrequent use of ivermectin in the very young. A review of this study in 5 years is planned to follow the trends described, and utilise the advances in faecal parasite diagnostics.

Acknowledgements: Microbiology staff of the six public hospital laboratories of the Northern Territory for helminth and cestode identification over the 11 years of this study.

Conflicts of interest and sources of funding: The authors state that there are no conflicts of interest to disclose.

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