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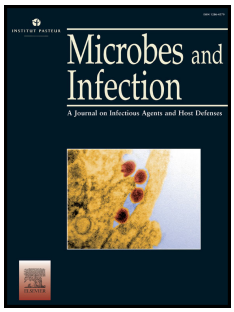

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Title: *Ascaris* and ascariasis

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Abstract

Ascaris lumbricoides and *Ascaris suum* are widespread parasitic nematodes of humans and pigs respectively. Recent prevalence data suggests that approximately 1.2 billion people are infected. Adult worms exhibit an overdispersed frequency distribution in their hosts and individuals harbouring heavy burdens display associated morbidity. In this review, we describe the parasite, its distribution and measures undertaken to control infection.

ASCARIS; EPIDEMIOLOGY; CONTROL; LIFECYCLE

Introduction

Ascaris lumbricoides, Linnaeus, 1758 and *Ascaris suum*, Goeze, 1782 are parasitic nematode (Family Ascarididae) infections of humans and pigs respectively.

The human roundworm *Ascaris lumbricoides* is one of the most common parasites in the world, infecting 1.2 billion people globally [1]. Infections are most commonly documented in sub-Saharan Africa, the Americas, China and east Asia [2]. The spectrum of disease associated with *A. lumbricoides* infection is known as ascariasis, and morbidity assessed as disability-adjusted life years (DALYs) is approximately 10.5 million [3]. Furthermore, morbidity with serious health consequences is observed in 122 million cases per year [3]. However, ascariasis is still considered a neglected tropical disease (NTD) [4].

Ascaris suum is a widespread parasitic nematode that causes infection in pigs with high prevalence rates in host populations [5, 6]. The prevalence of *A. suum* infection varies with geographical region and farm management practices but few swine herds are totally free of infection [7, 8]. Porcine ascariasis interferes with health and performance of pigs while resulting in reduced feed to gain ratios and liver condemnation incurring economic losses [9].

Taxonomy

Morphologically indistinguishable, human and pig *Ascaris* have been shown to differ by only six (1.3%) nucleotides in the first internal transcribed spacer (ITS-1) [10] and by 3-4% in the mitochondrial genome (mtDNA) sequence [11], indicating that the species are closely related at a phylogenetic level.

Even though both parasitic nematodes display strong affinity for their conventional hosts [12], experimental cross-transmission studies have demonstrated that *A. lumbricoides* can infect pigs and vice versa [13, 14]. In *A. lumbricoides* non-endemic areas in North America and Denmark, infected human hosts were found to harbour worms of pig origin [15, 16], indicating that pigs are a potential reservoir of infection for the human host population. However, molecular epidemiological studies in *Ascaris* endemic regions of Guatemala and China indicate that the level of cross-infection between host species is low or absent [11, 17, 18] and that gene flow is limited between/among different genotypes [17-19].

Life cycle of *Ascaris* species

Hosts contract *Ascaris* infection via the faecal-oral route. It is known that when infective eggs are ingested and hatch, *Ascaris* larvae develop in host parenteral tissues. A similar migratory route is observed in human and pig hosts, which is illustrated in the pig in Fig. 1. Following ingestion of infective ova, L_3 larvae covered by the L_2 cuticle [20], hatch in the small intestine and migrate to the caecum and proximal colon where they penetrate the mucosa [21]. The

larvae then migrate via the portal blood to reach the liver, where the L_2 cuticle is shed. After migration in the liver, the larvae advance to the lungs on days 6-8 p.i. [22]. The larvae penetrate the alveolar space and move to the pharynx where they are swallowed, resulting in returning to the small intestine on days 8-10 p.i. [22]. *A. suum* moult again to L_4 stage larvae in the small intestine on day 10 p.i. [23]. Larvae mature and reach sexual maturity in the small intestine, moulting again (L_5 stage larvae) on day 24 p.i. [23] (Fig. 1).

The hepato-tracheal migration takes place over a 10 to 14- day period after the uptake of eggs in pigs and humans respectively. Adult worms may reside in the intestines for approximately one year, but the majority of worms are expelled by the 23rd week of infection in pigs [24]. Male and female adult worms measure 15-25cm and 20-35cm respectively. Estimates of daily *Ascaris* female egg production generally are in the range of 200,000 eggs [25] but the number of eggs a female produces decreases with worm load [26]. Unembryonated ova enter the environment via the faeces and can remain viable in the soil for up to 15 years [27]. During embryonation, larvae undergo two moults in the egg [20].

Epidemiology of *Ascaris*

Ascaris of both human and pig origin exhibit an overdispersed frequency distribution, which results in the worms aggregating in few heavily infected hosts [22, 28-30]. This epidemiological

pattern in which 'wormy persons' [28] harbour disproportionately large worm burdens is also high within groups stratified by age and sex [29, 30].

Furthermore, studies involving the provision of anthelminthic treatment and subsequent observation of intensity of re-infection have shown that individuals tend to re-acquire similar worm burdens to those harboured before treatment. This phenomenon, which is termed predisposition, has been demonstrated in longitudinal studies for ascariasis in both humans [30, 31] and pigs [32], and can be detected over multiple rounds of chemotherapy [31]. The consistent variability in infection intensity observed between hosts generates the over-dispersed frequency distribution displayed in host populations discussed above.

The bases for heterogeneity of infection or predisposition are not yet fully understood. Much focus has been placed on investigating whether variation in infection intensity is a result of differences in environmental exposure to infection or susceptibility. Determinants of infection intensity may be divided into two categories – long-term effects that operate on the time-scale of the host life expectancy (e.g. host genetics, host socio-economic status), and short-term effects that operate on the time-scale of the parasite life expectancy (e.g. host acquired immune response). In an attempt to estimate the relative importance of long- and short-term effects on infection intensity, McCallum [33] used probability theory and concluded that both categories have an approximately equal contribution to the observed heterogeneity.

Differential exposure to infection in humans is difficult to quantify as there are many factors to consider [34, 35]. Kightlinger *et al.* [36] assessed exposure to infection in a population of children in S.E. Madagascar by environmental, demographic, behavioural, and socio-economic indicators. Results suggested that intensity of *A. lumbricoides* infection is influenced by gender-related behavioural and environmental factors that contribute to exposure. Furthermore, longitudinal studies in human host populations indicate that a range of socio-economic conditions such as housing conditions [37] and cultural practices such as unhygienic defecation practices [38] influence infection intensity.

Behavioural-mediated reduction in exposure with age is a likely determinant of the observed age-intensity profiles [39]. Adults are also known to harbour *A. lumbricoides* worms, but generally at a lower intensity than children [29, 31]. This has led to the suggestion that less marked aggregation in older age cohorts reflects a slow build-up of specific immunity or variation in susceptibility to infection over time. However, overdispersed worm frequency distributions are also recorded within age classes as age is not the only source of variation. Coupled with this, as Bundy [40] discussed, hosts with the greatest prior experience of infection are subsequently re-infected, indicating that acquired immunity cannot be the only primary determinant of variability in infection intensity.

McCallum [33] reported that genetic factors also play a significant role in predisposition to *Ascaris* infection. However Chan *et al.* [41] noted that environmental or behavioural features of the family household were found to be a major determinant of infection status. Nevertheless,

there are many lines of evidence indicating that the underlying mechanism of resistance/susceptibility to *Ascaris* infection is also influenced by host genetics, the host's immune repertoire (which is ultimately under genetic control) and concurrent infections. Knowledge of behavioural mediated acquisition of infection contributes to the development of control strategies to interrupt transmission. However, much focus is currently being placed on the genetic and immunological basis of host susceptibility to *Ascaris* infection, which is further discussed in the next review (Dold and Holland, current issue).

Strategies for control of *Ascaris*

For human hosts, there are three major strategies for the control of soil-transmitted helminths (STHs); reducing parasite intensity (and consequent morbidity) by means of improvements in sanitation, health education and anthelminthic treatment (chemotherapy) [42].

A number of parasite lifecycle characteristics and epidemiological patterns influence the design of control strategies for *Ascaris* infection. The production rates of ova combined with their durability and survival in the soil impacts on re-infection rates. Therefore, the long-term control and eradication of *A. lumbricoides* infection lies in the provision of sanitation for the safe disposal of human faeces [42]. Sanitation aims to interrupt transmission, prevent re-infection and gradually reduce worm loads. The construction of sanitary facilities may be encouraged through health education [43], which aims to stimulate changes in behaviour related to environment and family hygiene.

Since STH infections are coendemic, deworming programmes are targeted at all three helminth infections. WHO [44] endorsed the combined approach of integrated control of both schistosomiasis and STHs. Anthelminthic drug treatment programmes are aimed to reduce morbidity as opposed to eradicate helminths, which is not a feasible goal [44]. Regular systematic treatment is necessary due to high reinfection rates in endemic regions. For example, *A. lumbricoides* reached 55% of pre-treatment rates within 11 months [45]. Several approaches to treatment programmes exist; universal, selective and targeted treatment [46]. As described earlier, children tend to acquire heavier worm burdens and so are considered a suitable group for targeted treatment [47]. As summarised by Albonico *et al*. [46], WHO advise targeted treatment two to three times a year and once per year for school-age children with a prevalence exceeding 70% and between 50-70% respectively. In order to assess the optimal chemotherapy strategy and frequency for a given region, WHO [2] recommends rapid assessment of STH prevalence and intensity of approximately fifty children in five to ten schools per area. In response to WHO guidelines, Sturrock [48] demonstrated that assessing four to five schools, focusing on age cohorts most likely to be infected, in a given area provides a cost efficient strategy in identifying the communities which require mass treatment. Universal drug administration is recommended for communities where STH prevalence exceeds 20%, and those found to have a prevalence in excess of 50% are considered high risk [2]. While the frequency of chemotherapy is determined by prevalence, the cost of treatment at a given interval is $0.02-0.03 per individual [2].

Polyparasitism also requires consideration in design of chemotherapy strategies as there is concern that helminth infections have effects on the outcome of other infectious diseases that are considered pandemics. Similarly to other STH, the overlapping geographical prevalence of *A. lumbricoides* and diseases such as HIV, malaria and TB raises the possibility of causal links between these infections. A definitive result regarding whether *Ascaris* provides protection or is it antagonistic towards microparasite infection is however yet to be fully elucidated [49].

Transmission of *A. suum* among pig populations is dependent on factors such as housing systems, hygiene, management practices and anthelminthic treatment [6]. Therefore, as Roepstorff [8] discussed, there is a need for multivariate analyses encompassing a range of variables in order to assess the most important risk factors for controlling *A. suum* infection in pigs. Only one study encompassed a wide range of age categories [7] while assessing important risk factors. The variables tested that were significantly associated with *A. suum* infections were 'age-group', with large fatteners and gilts (young female swine) recorded to have the highest infection intensity [5], 'country', 'weaning age' as late weaning was associated with higher prevalence of infection, and 'water supply', which indicated that drinking facilities located in the lying area was a risk factor.

Ascaris associated pathology and morbidity

Ascariasis is the term used to describe the spectrum of disease symptoms observed in infected humans and pigs. Morbidity and mortality increases with worm burden [50], and those who

harbour light infections tend to be asymptomatic. Aggregation leads to relatively few individuals harbouring sufficient worms to precipitate life-threatening or severe morbidity [51]. As observed by Crompton [52], most *A. lumbricoides*-induced morbidity is borne by school-age children due to the age-related intensity patterns, discussed above and also due to their narrower intestinal lumen. Furthermore, as *Ascaris* larvae develop, different stage-specific antigens are observed [53] and various tissues are invaded, so therefore the effects of infection differ over the course of larval migration and development.

While the majority of infections are asymptomatic, an estimated 8-15% (120-220 million cases) of those infected with *A. lumbricoides* demonstrate associated morbidity [3, 43]. The manifestations of ascariasis can be broadly characterised into acute and chronic symptoms. Human hosts tend to experience acute lung inflammation, difficulty in breathing and fever as a result of larval migration through the pulmonary tissue. Abdominal distension and pain, nausea and diarrhoea are also characteristic symptoms of adult worm infection and chronic ascariasis [12]. Entangled adult worms have also been documented as leading to mechanical intestinal obstruction in 0.005-2 per 1000 infections per year [50].

Chan [3] described a model in which the worm burdens were separated into two threshold levels based on the disabilities experienced by the human hosts. The model facilitated calculation of the disability-adjusted life years (DALYs), which translates disabilities experienced into years of healthy life lost. As calculated by Chan [3], the DALYs lost due to ascariasis are 10.5 million, while the combined DALYs for the STHs, *Ascaris lumbricoides*, *Trichuris trichiura* and

hookworms are 39.0 million, which is higher than the DALYs estimated for malaria (35.7 million).

While *Ascaris* is most prevalent in areas of low socioeconomic status and thus poverty and malnutrition, studies indicate that *Ascaris* infection exerts a chronic influence on host nutrition [54]. Despite this, various intervention and clinical studies, the majority of which are focused on school children, demonstrated that infection is associated with appetite loss [55], lactose maldigestion [56] and impaired weight gain [55, 57]. Age intensity profiles indicate that those harbouring heavy infections are young children at vulnerable stages of growth and development, and for this reason the impact of infection on nutritional status remains of primary concern and interest. For logistical and ethical reasons, much focus has been placed on the effect of adult *Ascaris* worms on host growth. Recently, the impact of larval migratory ascariasis on host body weight was investigated in mice. Lewis *et al*. [58] noted a reduction in body weight during larval migration but also demonstrated that similarly to adult worms, this larvae-induced morbidity is related to infection intensity.

Porcine ascariasis is also known to interfere with the health and performance of pigs and is responsible for reduced feed to gain ratios resulting in considerable economic losses [9]. Similarly to human infection, porcine hosts display stunted growth and consume less food than uninfected controls [57, 59].

A. suum infections in young malnourished pigs provide an useful model for *A. lumbricoides* infection in children. *Ascaris*-infected pigs also display reduced food intake and growth rate [57, 59], and impaired lactase activity in the intestinal mucosa [59], all of which are significantly correlated with the intensity of infection [59]. Stephenson *et al.* [57] examined the effects of adult *Ascaris* infection in pigs on controlled diets and demonstrated that the effects on the nutritional status of the hosts was most evident in pigs on marginal protein diets. Furthermore, the efficiency of feed utilisation in *Ascaris*-infected pigs was decreased, which was a product of the observed reduction of the villar height to crypt depth ratio in the intestines.

There is also an association between helminth infection and a reduction in host cognitive abilities [reviewed by 60]. As reviewed by Bundy *et al*. [61], one must consider many confounding variables such as poverty, psychosocial stimulation and general health status when measuring the impact of health intervention on cognitive outcomes. Coupled with this, a range of differing tests and measurements of cognitive ability tend to be utilised in various intervention studies, which hinders accurate comparisons. In a mass-treatment scheme in Kenya, deworming did not improve academic scores. However, a 25% reduction in absenteeism was observed coupled with an improvement in school participation [62], indicating an impact of infection on performance and thus future economic productivity.

The impact of larval migration within human hosts remains an elusive topic for obvious ethical reasons [63]. An inflammatory reaction in the liver has been observed in *A. lumbricoides*- [64] and *A. suum*- [65] infected humans, pigs [66-69] and model organisms such as calves [70],

guinea pigs [71], rabbits [72] and mice [73]. In *A. suum* infections, white spots (WS) are white pathological lesions that are formed by the mechanical injury and inflammatory response induced by migrating larvae in the liver [69]. WS formation over the superficial hepatic surface and within the liver tissue is characteristic of porcine infections in response to larval migration through the liver [66, 68].

There are three types of WS observed in *A. suum*-infected pigs. The granulation tissue type WS (GT-WS) have been suggested to form along the larval migration routes (small GT-WS) or encapsulate trapped larvae (large GT-WS) [67-69] and therefore have been proposed to play a role in immunity to *A. suum* infection in pigs [68]. The larvae-induced GT-WS have been proposed as a precursor to the lymphonodular types WS (LN-WS) [68, 69], as the appearance of the latter on day 10 p.i. in pigs coincides with the healing of GT-WS [22]. While the described organ damage impacts on the health of the host, WS development and resultant liver scarring also leads to liver condemnation at slaughter, which has obvious economic implications.

Larval migration in the host lung tissue induces pulmonary distress in both porcine [74] and human [75] hosts. The respiratory distress experienced during pulmonary ascariasis is referred to Löfflers syndrome [76], which is a recognised eosinophilic disease [77]. In *A. lumbricoides* infection, dyspnoea (difficult or laboured breathing) and bronchospasm may be severe [77]. Severe dyspnoea has also been documented in porcine infections [73, 78]. Short dry coughs are also a typical feature of *A. suum*-induced respiratory distress in pigs [78] and have been reported in experimental infections of cows [79].

As illustrated here, while chronic adult infections have associated morbidity, important health consequences result from larval migration in both pigs and humans. Prevention of early infection induced morbidity is difficult to address due to an inability to investigate this life stage in humans for ethical reasons coupled with a lack of knowledge of infection status during migratory stages. Therefore, prevention of infection and re-infection is key as discussed earlier as it not only avoids the establishment of patent infections but also consistent hepatic and pulmonary distress.

Conclusions

As the most prevalent helminth infection, *Ascaris* is both important from and health and economic perspective. Despite the wide range of impacts on the health of hosts, *Ascaris* remains a neglected tropical disease. Furthermore, the parasite's persistence and prevalence presents difficulties regarding control strategies for the worm itself and concurrent infectious diseases. Therefore, further research on the mechanism of resistance to infection is required in order to facilitate future initiatives in reducing prevalence and infection intensities.

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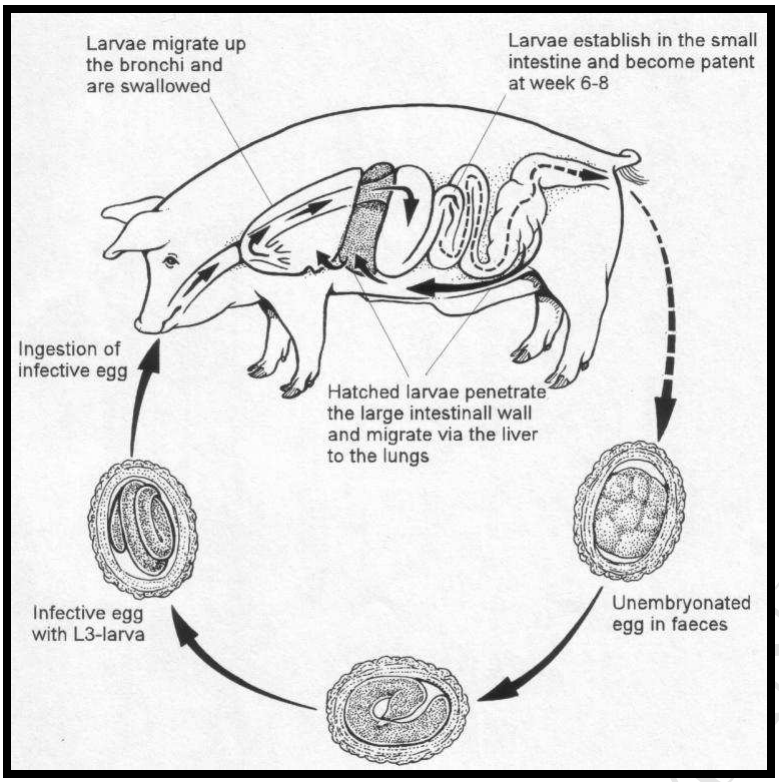

Figure 1. A schematic representation of the life cycle of A. suum in the pig (illustration by Wm P Hamilton CMI) [80]