Enterobiasis and its risk factors in urban, rural, and indigenous children of subtropical Argentina

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This is an Accepted Manuscript for Parasitology. This version may be subject to change during the production process. DOI: 10.1017/S0031182021001955

Abstract

A cross-sectional survey to assess the prevalence of *Enterobius vermicularis* infection and its associated factors among the child population of infant, preschool and school age in the urban, rural, and indigenous population of Iguazú city, in subtropical Argentina was presented. Additionally, the status of enterobiasis at country level was reviewed and analysed. *E. vermicularis* presence was assessed employing an oviscopic serial sampling technique. Statistical analysis of socio-demographic determinants was performed by Generalised Linear Mixed Models at individual, household, and community levels. Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines were used to gather national information about *E. vermicularis* prevalence spanning the decade 2010-2020. A total of 916 children from 470 families participated. Overall prevalence was 29.8%, with 25.3, 30.7 and 34.2% detected for children inhabiting urban, rural, and indigenous villages, respectively. The multi-level analysis showed that the presence of *E. vermicularis* was mostly determined by individual (e.g., age, playing habits, previous pinworm infection) and household level factors (e.g., family size, overcrowding conditions). Interestingly, WASH variables, such as waste disposal, analysed at community level were also important. Data were analysed to provide eco-epidemiological features of enterobiasis in a heterogeneous subtropical child population in the same territory but with different socio-sanitary realities. The importance of promoting multi-level actions against the determinants identified, to control this public health problem integratively was evidenced. The scoping review of national data updated the state of knowledge of this parasitosis, identifying risk determinants and gaps in knowledge at country level.

Key words: *Enterobius vermicularis*, Parasitic Intestinal Diseases, Child Health, Public health, Risk factors, Argentina.

Introduction

Enterobius vermicularis, also known as pinworm and one of the most prevalent intestinal helminths in humans, poses public health concerns worldwide. This parasite is widely distributed from the Arctic to the tropics, in developing and developed countries, and affects approximately half a billion people worldwide, predominantly preschool and school-aged children (Bethony *et al.*, 2006; Lukes *et al.*, 2005).

The earliest human infections were documented in prehistoric populations of both the Americas (Morrow & Reinhard, 2018; Reinhard *et al.*, 2016) and the Old World (Horne, 2002). Transmission of the helminth is by three principal pathways - hand-anus-mouth, inhalation of eggs, and retroinfection (Botero & Restrepo, 2012; Cook, 1994). The disease due to this parasite is known as enterobiasis or oxyuriasis. Although enterobiasis is asymptomatic in most infected adults, who typically have low worm burdens, it can cause significant morbidities in children, particularly in those with heavy infections (e.g., high worm burden), with neurological symptoms including nervousness, restlessness, irritability, and distraction, influencing child growth and wellbeing (Botero & Restrepo, 2012; Cook, 1994; Wendt *et al.*, 2019). The predominant clinical symptoms include anal itching and urinary tract infections especially in girls. The disease typically has a benign evolution with rare complications, and anthelmintic therapies are effective in the majority of cases (Botero & Restrepo, 2012; Cook, 1994; Georgiev, 2001). Ectopic locations are uncommon, but pinworms can occasionally be detected in the appendix (Hamdona *et al.*, 2016; Lala & Upadhyay, 2016; Levens *et al.*, 2014; Tapia & Muñoz, 2011), kidney, liver, lung, urinary tract, female genital tract (Cook, 1994; Craggs *et al.*, 2009; Das *et al.*, 2001; Kashyap *et al.*, 2014; Ngui *et al.*, 2014; Pigac *et al.*, 2017; Powell *et al.*, 2013), mesenteric lymph node (Zafar *et al.*, 2018), and caecal polyp (Elsaid *et al.*, 2014), which are all potential reservoirs of this parasite.

https://doi.org/10.1017/S0031182021001955

E. vermicularis is widely distributed, with an overall human prevalence of infection of about 20% worldwide, and up to 50% in children with socio-sanitary deficiencies (Botero & Restrepo, 2012; Cook, 1994; Georgiev, 2001). In Latin America, the prevalence of pinworm ranges between 2.5 and 60% (Bórquez *et al.*, 2004; Cazorla *et al.*, 2006; Knudson *et al.*, 2003; Requena-Certad *et al.*, 2002; Soto & Quiñones, 2015). Studies in Argentina, the second largest Latin American country after Brazil, reported 10-60% enterobiasis infections in schoolchildren from suburban and rural regions, with the most vulnerable being those living in socio-economically disadvantaged conditions (Bracciaforte *et al.*, 2010; Gamboa *et al.*, 2010; Lazarte S.G. *et al.*, 2006; Rivero *et al.*, 2018; Rivero *et al.*, 2017a; Soriano *et al.*, 2001). However, most studies have focused on reporting prevalence of infection and lack inferential analyses regarding risk-associated factors. Consequently, there is not sufficient understanding to inform specific surveillance and control at different scales.

Puerto Iguazú is a subtropical border city in the northeast region of Argentina, which has the highest poverty and indigence levels in the country (INDEC, 2016). Iguazú population is one of the fastest growing populations, with the highest percentage of children and young people in Argentina (INDEC, 2010). A wide spectrum of neglected and vector-borne diseases are endemic in the region and there is a pressing need for improved knowledge of disease burdens and associated risk factors to inform the control and prevention strategies for reducing negative impacts on health, social, and economic welfare (Orellano *et al.*, 2018a; Orellano *et al.*, 2018b; Rivero *et al.*, 2018; Rivero *et al.*, 2017a; Salomón *et al.*, 2009). Researchers emphasise the need for studies that identify specific determinants of each pathogen, elucidate predisposing factors and possible interactions between them (Rivero *et al.*, 2017a; Salomón *et al.*, 2009), and use such knowledge pragmatically to inform prevention and control strategies. The main objective of this study was to evaluate *E. vermicularis* prevalence, employing an oviscopic technique with serial sampling. Infection

https://doi.org/10.1017/S0031182021001955

and its relation with individual, family, and community factors were assessed integratively to explore associated variables, which individually or combined may determine the persistence of this parasite in urban, rural, and indigenous village settings. The goal was to unravel eco-epidemiological drivers underlying the heterogeneity in pinworm infections and risk factors among children in Puerto Iguazú, through an analytical approach capable to incorporate the potential complexity of these relationships at the different levels involved. The national status of enterobiasis was assessed and the analysis of the situation observed in terms of the public health implications was performed.

Materials and methods

Scoping review and eligibility criteria

To summarise the current stage of knowledge of *E. vermicularis* at country level, studies assessing the prevalence of the parasite through specific techniques for the detection of pinworm eggs (anal swabs or cellophane adhesive tape) during the last decade were systematically searched and gathered from four databases: LILACS, PubMed, Scopus, and Argentina SciELO. The search followed the PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) guidelines (Moher *et al.*, 2015), using '*Enterobius vermicularis'*, 'pinworm' AND 'Argentina' as keywords. References from 2010 to December 2020 were reviewed and analysed. The date of the last search was March 26, 2021. A manual search was also performed, and the reference lists of the original and review articles were examined. When more than one report was published based on the same study, only one was included in the review. Original articles published in journals with ISSN, in Spanish, Portuguese, or English languages, were included. Theses and summaries of the same authors of published papers, presented at congresses or in university thesis libraries were not included, to avoid duplication of partial and/or total results. We did not include literature

reviews or papers referring to a general prevalence of parasitosis or helminths without explicitly stating the prevalence of *E. vermicularis*.

All data extracted were organised in Microsoft Excel datasheets, and binary or multiple codifications were assigned according to survey location, study design, study population, and pinworm detection methodology. We used the country region classification defined by the National Institute of Statistics and Censuses of Argentina (INDEC) according to geographical data (e.g., population, housing, and economic aspects), climate, and political-territorial-administrative organisation: Pampa, Northwest (ANW), Northeast (ANE), Patagonia, Greater Buenos Aires (GBA), Cuyo, and the Antarctic region (Fig. 1) (INDEC, 2018; INDEC, 2019). The eligible publications reviewed about pinworm spanning the last decade were mapped to these regions (Table S1). Each study was geo-referenced and, when the locality name or geographical coordinates of the study area were not specifically described, the locality mentioned on the manuscript title was used to pinpoint the survey on the map.

Study area and population

Argentina is a South American country that extends from 22° to 55° south latitude and meridians 53° to 74° west longitude and presents a wide variety of climatic and socio-economic conditions (INDEC, 2018; INDEC, 2019; Rivero *et al.*, 2020). The present study was conducted in Misiones province, part of the Upper Parana Atlantic Forest eco-region and the most biodiverse area in Argentina (Bertonatti & Corcuera, 2000; Olson & Dinerstein, 1998). The population of this region is among the most impoverished and indigent in the country (INDEC, 2016). At its northwest point is located Puerto Iguazú, a subtropical city (25° 35‘52’’S and 54º 34’ 55’’W) bordering with Brazil and Paraguay. The urban area lacks town planning and has grown rapidly in recent decades (INDEC, 2016). Most houses are of cement, but precarious constructions of wood with sheet metal roofs are interspersed in most

of the city neighbourhoods. Although there are public services, not all the city has sewage or water networks. The rural area to the south is characterised by simple wooden buildings with dirt floors, and water from wells. Farm animals are raised for family sustenance as well as some small-scale crops of cassava, corn, other vegetables, and fruits. The indigenous group Mbyá-Guaraní is an ancient ethnicity with Amazonian roots, located to the east and southeast of Iguazú city; they constitute almost half of the indigenous population of Misiones province (INDEC, 2010), with very fragile sanitary and building conditions.

Study design

Subject recruitment

This cross-sectional survey was conducted from January 2018 to May 2019 in the urban, rural, and indigenous communities of Iguazú. Child sampling was randomised in the Public Health Care Centre (PHCC) areas in urban-periurban, rural, and indigenous villages of the municipality. From their population records, we estimated overall that about 6370 children <13 years of age were in the PHCC study areas. The minimum sample size was calculated using the formula for population-based surveys (Dean AG *et al.*), considering the population size, the expected frequency of enterobiasis (50%), and a confidence level of 95%, which corresponds to 10.14% of the children of urban and rural settings. In indigenous villages, after receiving authorisation from the "cacique" (the maximum political authority) of each village, recruitment included all the families who voluntarily agreed to participate (35.84% of the indigenous families). Houses were selected by simple random sampling and were visited by an interdisciplinary and intercultural team. Families with children under 13 years of age, without gastrointestinal symptomatology nor under parasitological treatment, were invited to participate. During household visits, the team provided information about the study, materials for sample collection (disposable collection kit), an epidemiological questionnaire, and

requested written informed consent for each child. In indigenous villages, all the activities were conducted in the mother tongue with the collaboration of the PHCC staff.

Sample collection

Parents were instructed to follow a serial perianal swab method shortly after the child's waking, before defecation or bathing, every other day during one week, to collect three samples in total. A collection kit was provided for each child. Parents were requested to place the gauzes in a plastic bottle containing formaldehyde 5%, previously labelled with the child's name and an identification code. Oral and written bilingual (Spanish/Mbyá-Guaraní) explanations about sample collection, as well as illustrated instructions, were provided with the collection kit. Field staff gathered the samples, following proper hygienic and bio-safety procedures. All samples were delivered to and processed at the laboratory of Parasitology and Zoonotic Diseases of the National Institute of Tropical Medicine (PZD-INMeT) in Puerto Iguazú.

Questionnaire

Demographic and socio-economic data were obtained with a pre-tested and structured questionnaire administered to children's mothers or legal guardians during house-to-house visits. The questionnaire surveyed personal and family variables (e.g., child gender and age, family composition, parents' work situation and educational level), including child's play, habits and personal hygiene (e.g., playing with soil, hand washing, thumb sucking, nail biting, anus washing), and household features (e.g., house building construction, water supply, excreta disposal, waste disposal). Information on previous enterobiasis, signs, and symptoms as well as previous treatments were also recorded for risk evaluation (Table 1). All

questionnaire data were double-entered into a database and cross-checked. The grouped analysis provided new categorical variables that were included in the analysis.

Assessing E. vermicularis infection

First, exhaustive macroscopic examinations were performed under a stereoscopic magnifier. Serial perianal gauzes were then subjected to centrifugation at 1500 rpm for 10 min and the pellet was observed under light microscopy. Examinations were performed over the entire area under the coverslip using a PrimoStar Zeiss optical microscope with dry 10X and 40X objectives. Identification of parasites was performed through the morphological and morphometric characteristics. Photographic and morphometric characterisations of adult worms were also registered. Samples were classified as positive if a worm was detected during the macroscopic analyses or if an egg or worm was observed in the pellet resulting from the swab-centrifugation. Microscopic observations were conducted in duplicate by two experienced microscopists. As a quality control, a random 10% of the total samples were re-examined by a senior laboratory researcher. Gauze analysis results were reported in triplicate: parents/legal guardians of the subjects received oral and written notification of the results, a copy was attached to each child's PHCC file, and a copy was kept in the INMeT research files.

Statistical analyses

Presence/absence of *E. vermicularis* was the main response variable. Variables characterising children's conditions, habits, and their local environments (Table 1) were included in the analysis as explanatory variables (fixed effects) in generalised linear mixed-effects models (GLMM), with the household as a random effect to consider the dependence of the data and nested factors (children belonging to each household) (Zuur *et al.*, 2009). To select the most

important variables (Magalhães *et al.*, 2011), univariate analysis was performed to describe general associations between the response and independent variables. To discern the most important combination of factors conditioning the persistence of *E. vermicularis*, the significant independent variables ($p<0.05$) from the univariate models were analysed by groups in subsequent multivariate GLMM analyses (see groups in Table 1). As we included children from contrasting populations (urban, rural, and indigenous), the effect of these populations and their potential interactions in relation to other independent variables were also evaluated. Before incorporating variables in multivariate models, multicollinearity inferred by the variance inflation factor (e.g., >5) was assessed (Zuur *et al.*, 2009). When two or more correlated variables were detected for candidate models, only the most significant variables in the univariate models were included in further models. The models obtained for each group of variables and their possible combinations were compared hierarchically using the Akaike Information Criterion corrected for small samples (AICc), to identify the best fit models containing only the most important and uncorrelated variables of each group (Burnham & Anderson, 2002). When more than one candidate model for each group was obtained, a model averaging these candidate models was used, and those variables that demonstrated a significant effect (i.e., 95% confidence interval of the β estimate that did not include zero) were retained. To know which combination of factors was the most important for explaining *E. vermicularis* infection in the children, as a final step we combined the selected models for each group in one global model, eliminating non-significant or correlated variables and comparing this global model with the group models by their AICc. The number of children per family was considered as a weight argument in these models to balance potential bias in household level factors caused by families with a high number of children (Zuur *et al.*, 2009). The presence of *E. vermicularis* was modelled as a binary response variable with a logit-link function. Statistical analyses were carried out with R software (R

Development Core Team, 2016) through library *lme4* (Bates *et al.*, 2015) and model comparisons, and averaging through library *MuMIn* (Barton, 2020). The odds ratios (OR) and their confidence intervals were calculated for each model using the R package *broom.mixed* (Bolker & Robinson, 2021) for evaluating the degree of association between the *E. vermicularis* infection and the independent variables, where $0 < OR < 1$ indicates a negative association, $OR = 1$ indicates lack of association, and $OR > 1$ indicates a positive association. Model fit and model assumptions were validated using the R package *DHARMa* (Hartig, 2021).

Results

Enterobiasis in Argentina during the decade 2010-2020

A total of 105 studies were initially identified, following PRISMA screening recommendations (Moher *et al.*, 2015). Of these, 26 studies reporting *E. vermicularis* presence at 39 localities from 2010 to 2020 met the inclusion criteria (Fig. S1) and were included in the subsequent analysis. This nematode was reported, through specific technique detection, in 11 of the 23 Argentine provinces. During these ten years, the presence of pinworm has been steadily reported in studies with up to four publications per year. Most surveys were performed in the child population up to 15 years of age in urban, periurban, and/or rural areas of different provinces of Argentina, and in indigenous child populations residing in the north region of the country. Overall, 12,629 children were evaluated during the decade with a median prevalence of 31.7%. The parasite was detected mainly in the Pampa and ANE regions, while ANW, Patagonia, Cuyo and GBA regions showed lower frequencies of *E. vermicularis* (Fig.1). The average prevalence in the different regions of the country varied between 18.45 and 39.7% over the ten-year period. The Pampa region ranked first, with some provinces such as Córdoba (Bracciaforte *et al.*, 2010b; Rustan *et al.*, 2011)

and La Pampa (Gamboa *et al*., 2010; Navone *et al*., 2017) with median values close to 50%. The ANW and Patagonia regions had lower enterobiasis values, close to 20% (Cociancic P *et al*., 2018; Dib *et al*., 2012; Dib *et al*., 2015; Navone *et al*., 2017).

Of the 26 articles reviewed, only 6 carried out inferential statistics. Regarding the main risk factors of *E. vermicularis* infection, several variables had been positively associated with thumb sucking, female gender, anal itching and grinding teeth (Rivero *et al*., 2018), children above 6 years old (Cociancic *et al*., 2018; Garbossa *et al*., 2013; Molina *et al*., 2011), onychophagia, children whose parents' literacy was incomplete (Cociancic *et al*., 2018; Garbossa *et al*., 2013), children whose mothers were the breadwinners (Gamboa *et al.*, 2014), and participants who lived in houses without piped water (Cociancic *et al*., 2019). Nevertheless, other studies in Argentina did not identify those risk factors when tested (Ferioli *et al*., 2020). Additionally, pinworm was reported as the most common parasite associated with protozoa parasites such as *Giardia intestinalis*, *Blastocystis hominis* and/or *Entamoeba coli* in all the country (Table 2). Child coinfection with *Hymenolepis nana* and *Trichuris*, hookworms and/or *Ascaris lumbricoides* were also reported (Table 2) (Bracciaforte *et al*., 2010a; Cociancic *et al*., 2018; Oyhenart *et al*., 2013; Pezzani *et al*., 2012; Rivero *et al*., 2018; Rivero *et al*., 2017; Zonta *et al*., 2019).

Socio-demographic characteristics of the study population

The enrolment process involved 980 children aged between 1 month and 13 years old. Of these, 93.5% (916) provided proper gauze samples, complete information in the socio-demographic questionnaires, and a signed informed consent. The children were from 470 families with a mean of 1.80 ± 0.91 children per family. There were 379 urban, 189 rural and 348 indigenous children corresponding to 201, 131 and 138 families, respectively. Overall, 55.02% of the study population were boys (n =504/916) and 44.98% girls (n =412/916), with

a mean age ± SD of 5.9 ± 3.6 years old. By age ranges, 25.55% were infants (INF, from 0 to 3 years old), 28.93% pre-school-age children (PSAC, from 3 to 6 years old) and 45.52% school-age children (SAC, from 6 to 13 years old). 34.61% (n =317/916) of the children were from large families with more than three siblings, with overcrowding present in 52.07 % (n =245/470) of the households.

The employment situation is precarious, and many families receive subsistence support from national subsidies. In indigenous villages, the employment circumstances are highly unstable, typically with temporary and casual work. Regarding household construction materials, 75.98% (n =696/916) of the children reside in unsatisfactory conditions, with no or only one main component (walls, ceiling, or floor) of cement, with mud and wood being the other predominant materials. Drinking water, excreta, and waste disposal were unsafe in 56.55% (n =266/470), 44.65% (n =210/470) and 55.46% (n =260/470) of the households, respectively. Farm animals were present in 52.62% (n =247/470) of the households, and 81.33% (n =382/470) of the families have dogs.

E. vermicularis prevalence in Iguazú children

The overall prevalence of pinworm infection detected through the serial perianal swab method among Iguazú children was 29.91% (n=274/916). There was a significant effect of the population on the presence of *E. vermicularis* ($\chi 2 = 6.44$, df = 2, p = 0.04). Indigenous children presented the highest prevalence at 34.48% (n=120/348), being those children 50% more likely to be infected than urban children (OR = 1.51, 95% CI: 1.10–2.08). In children in urban and rural areas, the prevalence was 25.86% (n=98/379) and 29.63% (n=56/189), respectively. The prevalence of *E. vermicularis* was slightly higher in girls than in boys [31.80% (n=131/412) vs 28.37% (n=143/504)]. The probability of infection increased with the age of the children ($\beta = 0.06$, z = 2.94, p< 0.001) and by age categories (PSAC: $\beta = 0.720$,

https://doi.org/10.1017/S0031182021001955

z = 3.38, p< 0.001; SAC: β = 0.880, z = 4.47, p< 0.001) (Tables S2). Considering all the Iguazú children, SAC children were 2.4 times more likely to be infected (35.25%, n=147/417, OR = 2.42, 95% CI: 1.64–3.56) than INF children (18.38%, n=43/234), followed by PSAC children (31.70%, n=84/265, OR = 2.06, 95% CI: 1.35–3.14) (Tables S2). Considering the age rates in each setting, urban PSAC and SAC children were 3.9 and 2.7 times more prone to infection than the INF children, respectively (Tables S2). However, in indigenous and rural settings, SAC children were the most affected group. Indigenous children presented higher probabilities in all age ranges (OR = 2.62, 95% CI: 1.21–5.65).

Household sanitary conditions

E. vermicularis infection was 30% less likely to occur in houses with satisfactory conditions (OR = 0.68, 95% CI: 0.48–0.96), 40% more likely to occur in houses with latrine or no excreta disposal system (OR = 1.42, 95% CI: 1.07–1.88), and 57% more likely where there was no waste collection service (OR = 1.57, 95% CI: 1.17–2.1), regardless of the population where the house was located (Tables S2). When combined, the waste disposal model alone was the most important model representing the effect of WASH variables (Tables S3 and S4).

In relation to family characteristics, the *E. vermicularis* infection risk increased by 88% in large families with more than 3 children (OR = 1.88, 95% CI: 1.41–2.52), and by 35% in families with overcrowding (OR = 1.35, 95% CI: 1.02–1.80), and also this infection was 2 times more likely to be present in families who declared prior knowledge of enterobiasis (OR = 2.04, 95% CI: 1.30–3.21) (Tables S2). The effect of large families varied according to the population, with the most important positive effect found on the large rural families (Tables S2). This interaction of population and family size combined with parent's previous knowledge constituted the most important model for this group of variables (Tables S3 and S4).

Child's habits and personal hygiene behaviour

All variables of this group were important predictors for *E. vermicularis* infection, independently of the population (Tables S2). Hand washing and anus washing habits showed protective effects reducing by 57 and 43% by *E. vermicularis* infection risk, respectively (hand washing OR = 0.43, 95% CI: 0.29–0.63; annus washing OR = 0.57, 95% CI: 0.39–0.83) (Tables S2). On the contrary, children with nail biting habits were two times more likely to be infected (OR = 2.00, 95% CI: 1.41–2.84), and 43% more likely if the children had thumb sucking habits (OR = 1.43, 95% CI: 1.03–1.98) (Tables S2). The combination of hand washing (not) and nail-biting habits constituted the strongest model for habits and personal hygiene behaviour variables (Tables S3 and S4).

Previous infections, signs and symptoms associated with E. vermicularis infection

Children previously treated for intestinal parasites were 2.4 times more likely to be infected by *E. vermicularis* (OR = 2.37, 95% CI: 1.49–3.76) than those never treated. A clear association was also found between pinworm infection and presence of the signs and symptoms evaluated (Tables S2). *E. vermicularis* was associated with sleep disorders (OR = 1.85, 95% CI: 1.27–2.68), anal itching (OR = 3.52, 95% CI: 2.53-4.91), grinding teeth (OR = 2.47, 95% CI: 1.67–3.64), and abdominal pain (OR = 1.57, 95% CI: 1.13–2.19) (Tables S2). The combination of anal itching and grinding teeth showed the strongest association in multivariate models (Tables S3 and S4).

Multi-level determinants of pinworm infection

The best final model, generated by combining the selected models by group, involved multilevel variables associated with pinworm infection and had the highest support among all

the tested models (Table 3 and Tables S3). At individual level, child age was the most important determinant of infection, but also it was important to consider the interaction between age categories and population. Additionally, previous pinworm infection, and nail baiting were variables of high importance included in the final model. At household level, family size (>3 children) and WASH variables (waste disposal) were also maintained as important predictors of parasite infection, but family size was important considering its interaction with child population (Table 3).

Discussion

The prevalence of *E. vermicularis* among children from a heterogeneous population in subtropical Argentina was reported and the epidemiological situation of this parasitosis depicted at country level. Based on studies reported from 2010 to 2020, the prevalence of *E. vermicularis* infection was above 30% (+/- 10%) across all Argentina. The child population with socio-economic vulnerabilities of the northeast and the Pampa regions was the most affected. Similarly, this analysis of enterobiasis infections among urban, rural, and aboriginal children of Iguazú, using the serial swab sampling basis technique, evidenced pinworms in almost 30% of the population. This represented a higher *E. vermicularis* prevalence among children than previous studies in the area (Rivero *et al.*, 2018; Rivero *et al.*, 2017a). Since *E. vermicularis* can affect the entire household, the finding in children provides a conservative estimate of parasite endemicity in the region.

The three sub-population groups studied had similar prevalence range of variability, but a statistically significant difference for the indigenous population. Importantly, the results showed that the gap between pinworm prevalence in children from urban and rural areas seemed to be minimal, coinciding with the global pattern reported in the last decades (Laoraksawong *et al.*, 2020; Moosazadeh *et al.*, 2017; Park *et al.*, 2005; Pezzani *et al.*, 2012).

The accelerated and unplanned growth of urban areas, resulting in communities living with multiple economic and sanitary constraints, contributes to the propagation and maintenance of infectious diseases (Eisenberg *et al.*, 2007). Nevertheless, the situation in indigenous villages highlights important epidemiological implications associated with the higher prevalence of enterobiasis in all age ranges of the child population, suggesting that it may be affecting the entire community. Indeed, they face precarious housing, socioeconomic difficulties, substandard hygiene and sanitation, a lack of or limited access to health care, as well as malnutrition (Navone *et al.*, 2006; Rivero *et al.*, 2018), a critical situation with poor prospects for near term changes. At the same time, the high prevalence of other pathogenic nematodes, such as hookworms and *Strongyloides stercoralis* affecting the villages, presents a complex scenario in these communities where children's health and development are constantly threatened (Brandelli *et al.*, 2012; Navone *et al.*, 2006; Rivero *et al.*, 2018). In this regard, the findings match those of many other studies which stress that, in communities in highly vulnerable conditions, it is necessary to conduct studies focusing on the whole community, and not simply on captive groups such as PSAC and SAC, with the object of proposing more suitable and effective control strategies (Brandelli *et al.*, 2012; Romero-Sandoval *et al.*, 2017; Song *et al.*, 2003). The holistic understanding of the interaction between diseases and individuals involves factors related to each individual (e.g., age, nutritional status, etc.), their proximal circumstances (e.g., family composition, household characteristics, etc.), their neighbourhood (e.g., socio-economic conditions), and the environment potentially acting at different levels (Eisenberg *et al.*, 2007; Mwangi *et al.*, 2016; Ross, 2012). In the present study, a hierarchical approach was used and made it possible to consider all these levels with the potential multiple factors involved concurrently, to account for the complexity of factors underlying pinworm transmission.

The multilevel modelling analysis of pinworm infection included individual, family, and household variables. Indeed, the final models, including the multiple factors comprising these levels, further support the paradigm of an integrative approach for understanding and preventing parasitic diseases. On an individual level, age group, personal hygiene habits (e.g., no hand washing), nail biting, and previous treatment were significantly associated with the presence of *E. vermicularis.* Host age is a determining factor in pinworm presence among children, consistent with recognition that enterobiasis risk is universally related to children's age, especially in the PSAC and SAC groups (Laoraksawong *et al.*, 2020; Remm & Remm, 2010). Interestedly, although PSAC and SAC-age children were the most parasitised group, children under three years old showed higher prevalence, suggesting the importance of adding this group when assessing the epidemiology and interventions of entero-parasitosis (Pullan & Brooker, 2008; Worrell *et al.*, 2016). This may be related to age-specific hygiene and playing habits that facilitate greater contact with the transmission routes of parasite infective stages. Hygiene habits, especially related to hand washing, are not well ingrained in the infant population, and are a substantial determinant of parasite acquisition (Curtis *et al.*, 2009; Gelaw *et al.*, 2013). Similarly, children who bite their fingernails are at higher risk for ingesting eggs from the environment, which is another risk factor of pinworm infection (Cook, 1994; Cranston *et al.*, 2015; Rivero *et al.*, 2017a; Sung *et al.*, 2001).

Host traits that may promote higher susceptibility are closely related with host exposure to risk factors and immune defense (Vaumourin *et al.*, 2015). Remarkably, children having had past pinworm infection was an important predictor for their current infection, suggesting that intrinsic or extrinsic conditions favouring its maintenance remain unresolved (Rivero *et al*., 2017; Rivero *et al*., 2018). Due to the efficiency and widespread nature of the parasite transmission, total eradication of pinworm is difficult and very unlikely. Elimination of the

parasite from a family often poses problems, and reinfection is common even after deworming (Botero & Restrepo, 2012; Cook, 1994; Moffa *et al.*, 2019).

Among the signs and symptoms potentially related to enterobiasis reported by mothers, anal itching and grinding teeth showed a clear relation with *E. vermicularis*. Additionally, abdominal pain analysed as a single symptom was significantly related to pinworm presence. Indeed, this parasite can cause severe abdominal pain, mimicking appendicitis, and numerous case reports worldwide act as cautionary reminder of the importance of considering potential *E. vermicularis* in children with abdominal pain (Dunphy *et al.*, 2017; Efared *et al.*, 2017).

Thus, although the common infection has a good prognosis, educational interventions at community level and the dissemination of epidemiological knowledge in the medical sphere are essential (Kang *et al.*, 2012; Kim & Yu, 2014; Nithikathkul *et al.*, 2005; Rivero *et al.*, 2017b). In the case of ectopic presentations, diagnosis may be difficult, mainly because of lack of clinical suspicion. These actions thus contribute to reducing parasite prevalence and reinfection and enable medical professionals to better complete the clinical diagnosis and guide treatment.

Considering the three populations under study, family variables such as size and household overcrowding were identified as risk factors. Large family size (with more than three children) was associated with a higher presence of *E. vermicularis*, and school age siblings also increase pinworm infection risk (Laoraksawong *et al.*, 2020; Rivero *et al.*, 2017a; Sung *et al.*, 2001). This pattern is closely related with overcrowding, usually associated with the higher prevalence and chronicity of intestinal parasite infections (Duflo *et al.*, 2012; Halpenny *et al.*, 2012; Rivero *et al.*, 2017a).

Although in the study population, household deficiencies were evidenced to a greater or lesser degree according to the settings - indigenous villages, rural, or urban - when WASH variables (water origin, excreta and waste disposal) were considered, only poor waste

management had a strong effect related to parasite infection at household level in the final model. In the study area, waste generally accumulated for subsequent burning and burying near the houses. Although it is difficult to associate this variable with pinworm morbidity, it is well known that improper waste management and disposal has a ripple effect on the environment, and can greatly affect the health of the population living near the polluted area, contributing to the spread of diseases (UNEP, 2009) (Makoni *et al.*, 2004; Odonkor *et al.*, 2020). Therefore, the elimination of inappropriate practices, and policy inputs on strategies to ensure a clean and safe environment through proper disposal, are required. The design of new models for effective waste management in the study area will improve the household environment and, therefore, community health.

In conclusion, it is evident that a combination of elements acts at different levels for the persistence of *E. vermicularis* in urban-rural and indigenous villages in subtropical Argentina. Implementing a solid statistical inference with a multilevel analysis certainly allowed an integrative understanding of this infectious disease. Enterobiasis is one of the most prevalent, but underrated, parasitic diseases in children in Argentina. It has a negative impact on children's development and welfare, especially in vulnerable populations and it should therefore not be regarded merely as a nuisance. Identifying the determinants of infectious diseases affecting these sensitive populations, as well as their interactions, presents the challenge of formal interdisciplinary languages for modelling complex realities. Awareness of socio-economic conditions at household level, and of children's healthcare are of great relevance. Parents' and children's exposure to poverty and associated stressors demand the commitment of scientists, policy makers, and practitioners to alleviate the costs of poverty for human development. From the public health perspective, the great impact that needs to be achieved involves bridging the gap between knowledge and action.

Although analysing studies by country regions shows trends in pinworm prevalence, it is important to note that they do not represent the whole region but only the sites analysed and that there may be biases in representativeness. Future research could explore factors that underlie the reality of each region. Associated data about immunity to co-infections, anaphylaxis-autoimmunity, and physical-cognitive development framed in each region will substantially increase the knowledge of the impact of this pathogen in Argentina.

Strategies need to be developed or validated to mitigate adverse epidemiological situations, promoting operational solutions at local level and respecting cultural diversity. Short and long-term implementation strategies will be guided by evaluating the differential impact of mass and targeted deworming, by direct actions to tackle the risk factors detected, and by the combination of these in different settings. Undoubtedly, the framework to evaluate the effectiveness, sustainability, and scalability of those strategies highlights the substantive methodological challenges that need to be addressed to promote sustained health monitoring.

Supplementary material

Supplementary Figure 1. This describes the procedure used for selecting the articles included in this study according to PRISMA.

Supplementary Table S1. *E. vermicularis* in Argentine human surveys from 2010 to 2020.

Supplementary Tables S2. Simple GLM models.

Supplementary Tables S3. Model selection process for the multivariate models for each group of variables.

Supplementary Tables S4. Multivariate final models selected for each group of variables.

Acknowledgements

We would like to thank the PHHC health workers & families who participated. We are grateful to all the indigenous health promoters for the mother tongue translation and their collaboration in the field. We thank the ESRI Conservation Program and the Society for Conservation GIS for software licences.

Author Contribution

MRR conceived, designed and supervised the study. MRR, CF and MMS conducted investigation and data gathering. MRR and CDA performed data curation, statistical analyses and designed the maps. MRR, CDA and CF wrote the article. SL and KT performed visualization and validation activities. MRR, CDA, SL, KT and ODS reviewed and edited original draft.

Financial Support

This research was funded by the National Scientific and Technical Research Council, CONCIET PIP-11220150100741CO and the National Agency for the Promotion of Science and Technology ANPCyT (FONCyT), PICT-2017-1125 and PICTO-2017-0094 to M.R.R and the National Ministry of Health.

Conflicts of Interest

The authors declare that they have no conflict of interest.

Ethical Standards

Ethical approval was obtained from the Bioethical Committee of Misiones province, Argentina. The Helsinki Declaration and national regulations concerning personal data protection (national law No. 25.326), Indigenous Policy, and Support to Indigenous

Communities (national laws Nos. 23.302 and 24.071) were followed. Treatment was provided to the children detected positive and to their families following standard clinical practice according to the National Ministry of Health and under the guidance of a physician.

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Table 1 Socio-demographic variables analysed at different levels for explaining pinworm infections.

Group of variables	Variable	Description and levels
Population	Population	Population to which the children belong: Urban, Rural, or Indigenous
Children	Sex	Male vs. female children.
	Age (continuous)	Children's age in years.
	Age categories	INF (< 3 y), PAC (from 3 to 6 y), SAC (from 6 to 13 y).
WASH	House conditions	Satisfactory vs. Unsatisfactory housing conditions. Variable created considering house building materials.
	Water source	Origin of drinking water. Safe (tap water) vs. unsafe water source (well pump, springs).
	Excreta disposal	Excreta disposal method: Safe (cesspool) vs. unsafe (latrine or open space).
	Waste disposal	Waste disposal: Safe (waste collection service) vs. unsafe (trash burning or burying).
Animals	Dogs	Presence vs. absence of dogs
	Farm animals	Presence vs. absence of farm animals
Family	Large families	Families with more than 3 children vs. families with 3 children or less
	Overcrowding	More than three children per bedroom in the house.
	Parent's knowledge	Parent's knowledge of enterobiasis
Habits	Hand washing	Child with the habit of hand washing
	Anus washing	Child with the habit of anus washing
	Nail biting	Child with the habit of nail biting

	Thumb sucking	Child with the habit of thumb sucking
Previous infection	Previous pinworm infection	Children whose mother reported a previous pinworm infection at some point of their life
Symptoms	Sleep disorders	Child whose mother observed sleeping disorders
	Anal itching	Child whose mother observed anal itching
	Grinding teeth	Child whose mother observed grinding teeth
	Abdominal pain	Child whose mother observed abdominal pain

Table 2 Most common helminths and protozoan parasites reported in association with *E. vermicularis* in Argentine regions during 2010-2020.

	***E. vermicularis* in Argentine regions**					
Parasites	Pampa	Northwest	Northeast	Patagonia	GBA	Cuyo
Non-pathogenic protozoa						
Entamoeba coli	•		•	•	•	
Pathogenic protozoa						
Blastocystis hominis	•	•	•	•	•	•
Giardia intestinalis	•		•			
Helminths						
Hymenolepis nana	•	•	•			
Ascaris lumbricoides			•			
Trichuris trichiura	•					
Strongylides stercoralis			•			
Hookworms	•	•	•			

https://doi.org/10.1017/S0031182021001955

Table 3 Simple GLM models analysing the effect of different variables on the presence of Enterobius vermicularis (univariate models), and the potential interaction of each variable with the population where the children live (univariate models by population). Significant variables marked in bold (p <0.05). The columns to the right show the estimated odds ratio (OR) and the 95% confidence interval.

*Model**	*Estimate*	*Std. Error*	*z value*	*Pr(>|z|)*	*OR*	*Conf. low*	*Conf. high*
(Intercept)	-1.973	0.329	-5.990	<0.001	**0.139**	**0.073**	**0.265**
Population (Rural)	-0.324	0.536	-0.604	0.546	0.723	0.253	2.070
Population (Indigenous)	0.179	0.441	0.405	0.686	1.200	0.503	2.840
Age (PAC)	**1.383**	**0.374**	**3.693**	**0.000**	**3.990**	**1.910**	**8.300**
Age (SAC)	**0.983**	**0.359**	**2.736**	**0.006**	**2.670**	**1.320**	**5.410**
Waste disposal (Burning or burying trash)	**0.391**	**0.177**	**2.213**	**0.027**	**1.480**	**1.050**	**2.090**
More than 3 children	0.076	0.318	0.238	0.812	1.080	0.578	2.010
Hand washing	**-0.833**	**0.197**	**-4.236**	**<0.001**	**0.435**	**0.296**	**0.639**
Nail biting	**0.644**	**0.191**	**3.371**	**0.001**	**1.900**	**1.310**	**2.770**
Previous pinworm infection	**0.790**	**0.257**	**3.074**	**0.002**	**2.200**	**1.330**	**3.650**
Age (PAC): Population (Rural)	-0.445	0.632	-0.704	0.481	0.641	0.186	2.210
Age (PAC): Population (Indigenous)	**-1.513**	**0.512**	**-2.954**	**0.003**	**0.220**	**0.081**	**0.601**
Age (SAC): Population (Rural)	0.276	0.601	0.460	0.646	1.320	0.406	4.280
Age (SAC): Population (Indigenous)	-0.347	0.469	-0.739	0.460	0.707	0.282	1.770

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More than 3 children:							
Population (Rural)	**1.302**	**0.564**	**2.311**	**0.021**	**3.680**	**1.220**	**11.100**
More than 3 children:							
Population (Indigenous)	0.559	0.414	1.351	0.177	1.750	0.777	3.930

* DHARMa nonparametric dispersion test: value = 1.005, p-value = 0.896, Deviation = n.s.; Uniformity k-test: D = 0.019, p-value = 0.893, Deviation = n.s.; DHARMa outlier test: outliers at both margin(s) = 7, observations = 916, p-value = 1, Deviation = n.s.

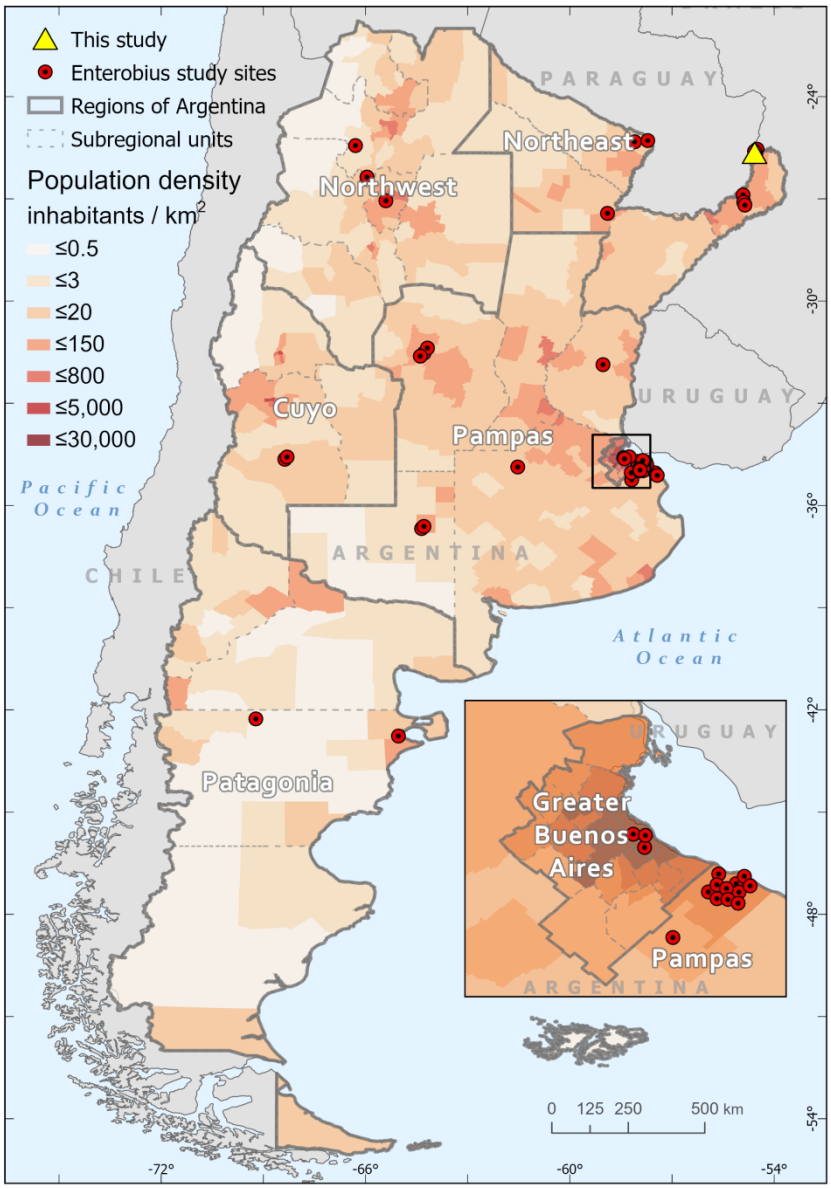

Fig. 1. Distribution of study sites of eligible publications and the present study by INDEC region of Argentina. Circles indicate *E. vermicularis* in Argentinian human surveys from 2010 to 2020. Insert shows studies in Buenos Aires, where there was the highest number of surveys about this issue. The study area of the present work, the Iguazú Municipality located in the tri-border area of Argentina, Brazil, and Paraguay, is depicted as a triangle. The map of Argentina was constructed using population density data from the last National Census, INDEC 2010, and was created with ArcGIS Pro 2.8 (www.arcgis.com).