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Seroprevalence of five neglected parasitic diseases among immigrants accessing five infectious and tropical diseases units in Italy: a cross-sectional study

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4

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112 **Abstract**

113 *Objective:* This multicentre cross-sectional study aims to estimate the prevalence of five
114 neglected tropical diseases (Chagas disease, filariasis, schistosomiasis, strongyloidiasis,
115 toxocariasis) among immigrants accessing health care facilities in five Italian cities
116 (Bologna, Brescia, Florence, Rome, Verona).

117 *Methods:* Individuals underwent a different set of serological tests, according to country of
118 origin and presence of eosinophilia. Seropositive patients were treated and further
119 followed up.

120 *Results:* A total of 930 adult immigrants were enrolled: 477 men (51.3%), 445 women
121 (47.9%), 8 transgender (0.8%); median age was 37.81 years (range 18-80). Most of them
122 were coming from the African continent (405/930, 43.5%), the rest from East Europe,
123 South America and Asia. A portion of 9.6% (89/930) were diagnosed with at least one of
124 the infections under study. Seroprevalence of each specific infection varied from 3.9%
125 (7/180) for Chagas diseases to 9.7% (11/113) for toxocariasis. Seropositive people were
126 more likely to be 35 to 40 years-old male and to come from South East Asia, Sub-Saharan
127 Africa or South America.

128 *Conclusions:* The results of our study confirm that neglected tropical diseases represent a
129 substantial health problem among immigrants and highlight the need for addressing this
130 emerging public health issue.

131

132

133 **Introduction**

134 The World Health Organization (WHO) defines the neglected tropical diseases (NTDs) as
135 a diverse group of infections mainly affecting poor populations, increasing poverty, and
136 having a low priority in the political and scientific agenda [1].

137 Human migration is a key factor in the appearance/re-appearance of NTDs in non or
138 former endemic contexts [2] [3]. We live in an era of unprecedented human mobility, with
139 approximately 232 million international migrants and 740 million internal migrants
140 worldwide [4]; Eurostat estimated that a total of 3.4 million people migrated to one of the
141 European Community countries in 2013; half of them came from non-member countries
142 [5]. In 2014, immigrants accounted for the eight per cent of the total Italian resident
143 population [6]; another 326,000 undocumented immigrants and refugees were present in
144 Italy. [7].

145 Immigrants are generally young and in good health conditions [8], nevertheless, the
146 prevalence of some infectious diseases may be significant among immigrants, as a result
147 of the wide diffusion of these conditions in their countries of origin [9] and the further
148 exposure during migration [10] [3]. Many infections, including several NTDs, may be
149 asymptomatic and hence remain undiagnosed [11]. As a consequence, seropositive
150 individuals can develop chronic forms (e.g. Chagas disease, schistosomiasis), fatal
151 complications (e. g. Chagas disease, schistosomiasis or strongyloidiasis) and can
152 potentially transmit the disease [11].

153 The research on the burden of communicable diseases among immigrants in Western
154 countries mainly focuses on HIV, tuberculosis and viral hepatitis [8] [12]. NTDs were rarely
155 addressed, possibly because they are often asymptomatic and have a relatively low
156 transmission in the absence of environmental and biological reservoirs/vectors. Moreover
157 in most of the European countries there is no systematic mandatory regulation regarding
158 NTDs reporting and surveillance [13]. Given the considerable immigration flows to Italy
159 and the scarce information on the relevance of the NTDs, seldom considered at hospital
160 level, this study aims to estimate the seroprevalence of five NTDs (Chagas disease,
161 filariasis, schistosomiasis, strongyloidiasis and toxocariasis) among immigrants attending

162 hospitals and relative outpatient clinics in five Italian cities: Bologna, Brescia, Florence,
163 Rome, and Verona.

164

165

166 **Methods**

167 *Study population, data collection and patient management*

168 A cross-sectional survey was performed in five Italian infectious and tropical diseases units
169 located in five different hospitals (Bologna University Teaching Hospital; Florence
170 University Teaching Hospital; Hospital Sacro Cuore – Negrar, Verona; Spedali Civili
171 General Hospital, Brescia; L. Spallanzani University Teaching Hospital, Rome) and in one
172 outpatient clinic for undocumented immigrants (Brescia Local Health Authority outpatient
173 clinic). In the hospital setting, patients were usually referred from primary care, Emergency
174 Departments or other secondary care services; they were either inpatients or individuals
175 with chronic infections followed-up in specialised outpatient clinics.

176 Individuals who attended any of the above mentioned centres for any reason in the study
177 period (November 2012 to November 2014) and who were born in an endemic country
178 (see online appendix Annex 1 for details), older than 18 years and with sufficient
179 knowledge of Italian or a timely access to a linguistic mediator, were eligible. In each
180 clinical centre one or two investigators were responsible for offering participation to the
181 project to each eligible patient seeking care during any of their routine clinical activities.
182 After signing the informed consent, enrolled patients underwent a different set of
183 serological tests according to the criteria reported in online appendix Table 1. The choice
184 of the infections was based on the most common areas of origin of immigrants in Italy, the
185 potential severity of the disease if not treated, the availability and quality of diagnostic
186 tools, the amenability to treatment and the potential for spreading in the community. The
187 definition of endemic country for a certain infection was based on the WHO geographical

188 classification of NTDs [14] (see online appendix Annex 1 for details). For filariasis, only
189 endemic countries for lymphatic filariasis, onchocerciasis and loiasis were included.
190 Serology for toxocariasis and filariasis was limited to individuals with eosinophilia. These
191 two diseases usually present with a raised eosinophil count [15]. However, in order to
192 increase case detection, eosinophil cut-off level was set at 300/ μ L instead of 450-500/ μ L,
193 as routinely suggested [15], for its good positive predictive value for helminthiases [16].
194 Concurrently, clinical and socio-demographic information, including country of origin, list of
195 visited countries, time since arrival, and educational level were collected. The investigators
196 offered treatment and follow-up to seropositive patients, while they supplied seronegative
197 individuals with the results of their tests. The centres elaborated operational guidelines for
198 the management of each disease which were made available on the study website.
199 Study protocol was approved by the ethics committee of the coordinating site (Bologna
200 University Teaching Hospital) under the resolution number 124/2012/O/Oss and by those
201 of all other participating units.

202

203 *Microbiological diagnosis procedures*

204 A sample of 12 ml of venous blood was collected from each participant. Blood samples
205 were centrally tested at the Service of Epidemiology and Laboratory for Tropical Diseases
206 of the Hospital Sacro Cuore – Don Calabria, Negrar in order to reduce inter-laboratory
207 variability. Serum samples were tested for specific antibodies using commercial
208 immunoenzymatic assays according to manufacturer's instructions. The qualitative
209 presence of antibodies for *Trypanosoma cruzi* (etiologic agent of Chagas disease) was
210 tested employing two enzyme-linked immunosorbent assays (ELISA), one based on
211 recombinant antigens ("BioELISA Chagas", Biokit, Lliça d'Almunt, Spain), the other based
212 on crude antigens ("BioELISA Chagas III", BiosChile, Santiago, Chile). For the other
213 infections a single ELISA was used ("Filariasis ELISA kit", Bordier Affinity Products SA,

214 Crissier, Switzerland, for filariasis; “*Schistosoma mansoni* ELISA kit”, Bordier Affinity
215 Products SA, Crissier, Switzerland for schistosomiasis; “Strongyloidiasis ELISA kit” based
216 on *Strongyloides ratti* antigens, Bordier Affinity Products SA, Crissier, Switzerland for
217 strongyloides; “DRG *Toxocara canis* ELISA”, DRG Instruments GmbH, Marburg,
218 Germany, for toxocariasis).

219

220 *Statistical analysis*

221 Categorical variables were described through frequencies and the median and the ranges
222 were used to describe age. Countries of origin were subsequently grouped into 11 regions
223 following the Geosentinel classification [17]. This choice relies on the fact that Geosentinel
224 system splits the globe into a higher number of regions (eleven) than WHO (six), with more
225 precise identification of risk areas.

226 Prevalence point estimates and their 95% confidence intervals were obtained. Chi-square
227 tests were performed to assess differences between groups. Data were managed and
228 analysed using STATA 14.1.

229

230

231 **Results**

232 *Description of the study population*

233 From November 2012 to November 2014 a total of 930 individuals were enrolled across
234 the six centres. Two thirds of them were outpatients. Due to refused consent or scarce
235 knowledge of Italian/lack of linguistic mediator, 4.9% (48/978) of the individuals were not
236 enrolled.

237 Socio-demographic information of the enrolled population is summarized in online
238 appendix Table 2. The male-to-female ratio was 1:1, and the median age was 37.8 years
239 (range 18-80); almost half of the participants had been living in Italy for more than 10

240 years. Individuals coming from the African region represented 43.5% of the total (405/930);
241 other frequent areas of origin were Eastern Europe (197/930, 21.2%), South and Central
242 America (177/930, 19.0%) and Asia (142/930, 15.3%). More than a half of patients
243 declared a medium or high level of education (high school diploma or degree). The socio-
244 demographic profile of the individuals varied slightly across the six centres. In the clinic for
245 undocumented immigrants in Brescia, enrolled subjects were younger than the total
246 population (median age of 35.2 versus 37.8 years, age range of 18-64 versus 18-80) and
247 their time since arrival was slightly shorter (50.9%, 56/110, of them arrived in the last four
248 years versus 31.3%, 290/930, in the total). Differences across the centres in terms of
249 origin might mirror the differing immigrant flows to the Italian cities: despite the high
250 presence of African immigrants in the whole sample, individuals enrolled in the Roman
251 hospital were mainly South Americans and the ones enrolled in Bologna mainly came from
252 Eastern Europe.

253 A white blood cell count was available for 583 individuals: among them, 19.4% (113) had
254 eosinophilia.

255

256 *Seroprevalence of the neglected infectious diseases*

257 Among the 930 enrolled individuals, 96 new infections were detected: 42 cases of
258 strongyloidiasis, 31 of schistosomiasis, 11 of toxocariasis, 7 of Chagas disease, and 5 of
259 filariasis. Eighty-nine patients were diagnosed with one or more NTDs, which leads to an
260 overall seroprevalence of 9.6% (95%CI 7.8-11.6) in the study population. Seven
261 individuals had two infections simultaneously. Across the centres the prevalence varied
262 between 6.3%, 7/110, (in Brescia clinic for undocumented immigrants) and 15.3%, 30/193,
263 (in Verona).

264 Seropositive individuals were mostly men (M:F=2:1) with a median age of 38.8 years
265 (range 21-78). The seroprevalence was twice as high in men as in women (p-value<0.05)

266 for all infections except for Chagas disease. The Geosentinel region with the highest NTDs
267 prevalence was South East Asia, followed by Sub-Saharan Africa and South America.

268 Among the 189 patients who were known to be HIV positive, 14 (7.4%) were also
269 seropositive for at least one of the NTDs under study (8 cases of strongyloidiasis, 4 cases
270 of schistosomiasis, 2 cases of toxocariasis and 1 case of Chagas disease).

271 Global seroprevalence, women to men ratio and regions with highest prevalence are
272 shown in Table 1. Detailed prevalence estimated by infections and Geosentinel regions
273 are listed in online appendix Table 3.

274

275 **Discussion**

276 Approximately one out of 10 individuals in our study was seropositive for at least one of
277 the infections. This figure represents a considerable burden given the potential
278 consequences of these conditions. In particular, strongyloidiasis and Chagas disease can
279 lead to chronic infections, which might represent a serious threat for the individual and the
280 health systems [18]. Strongyloidiasis is responsible of the hyperinfection syndrome, a rare
281 life-threatening complication that mainly affects immunosuppressed individuals, thus early
282 detection and treatment are particularly relevant [19]. Similarly, the potential
283 transmissibility of Chagas disease outside endemic areas, through blood transfusions,
284 organ or tissue transplants, or mother-to-child, highlights the importance of its early
285 detection [20]. Furthermore, most of these infections are treatable with affordable and
286 generally well-tolerated therapies, especially when compared to the severity of the
287 untreated consequences [21].

288 Interestingly, we noticed a higher prevalence of the five neglected infections among
289 patients coming from South East Asia, Sub-Saharan Africa and South America, suggesting
290 that immigrants coming from these areas are most at risk. However, this broad geographic
291 subdivision may mask differences at country level which we were not able to account for,

292 given the limited sample size. The prevalence of all infections was twice as high in men as
293 in women (p -value <0.05) but Chagas disease. A potential higher environmental and
294 working exposure risk for intestinal parasites and other vector-borne infections among
295 male immigrants can contribute to explain this finding [22]. Age and time since arrival in
296 Italy were not associated with the presence of infections.

297 These results are in line with the findings of similar studies carried out in Spain [8] [23],
298 except for Chagas disease prevalence, which was much higher in the Spanish samples.
299 This difference may be explained by the larger proportion of enrolled Latin American
300 subjects in the Spanish studies, as a consequence of a different migration pattern and the
301 availability of widespread screening programs. A cross sectional study carried out in
302 Australia [11] among recent immigrants and two others conducted in the United States in
303 refugees [9] [24] reported a higher prevalence of intestinal parasitic infections than in our
304 study. These figures may be explained by the different population under study and by our
305 diagnostic approach based on antibody detection. The mentioned studies mainly enrolled
306 refugees and recent immigrants and used microscopic examination of the stools,
307 identifying also parasites for which no serological test is available.

308 As already reported by others [25], we noticed a significant seroprevalence of NTDs in the
309 subgroup of patients with a known HIV infection. In this subgroup of patients treatment
310 should be strongly recommended, because of the risk of severe complications especially
311 in the case of strongyloidiasis and Chagas disease [25].

312 In our study, the proportion of individuals with an increased eosinophil count was in line
313 with other studies [26] [15], despite a possible overestimation due to the lower cut-off level
314 for an abnormal eosinophil count. Eosinophilia generally occurs in approximately 10% of
315 individuals returning from the tropics [15], and a prevalence up to 30% is often reported
316 among immigrant populations [26]. In this last group helminthic infections are the
317 commonest identifiable cause of eosinophilia, accounting for 14% to 64% of the total

318 cases [15]. Among those who were screened for strongyloidiasis, positive patients were
319 more likely to have a high eosinophil count (data not shown). This result confirms what
320 was previously found and emphasizes the importance of investigating the presence of *S.*
321 *stercoralis* among immigrants, particularly in presence of raised eosinophil levels [15].
322 Whilst for Chagas disease and schistosomiasis serology is deemed to be a valid screening
323 tool [8], there is no standard method for the detection of other intestinal parasites [27].
324 When stool microscopy had been used for screening purpose, the prevalence was found
325 to be relatively low [8] [23]. Amongst intestinal parasites we focused on strongyloidiasis,
326 because of its potentially fatal complications in immunosuppressed populations and to its
327 long-term persistence in the host [28].
328 The main limitation of the study is its generalizability. The enrolment took place at hospital
329 level and not at the community level; this means that our results may not be entirely valid
330 for the general immigrant population. Individuals who access the health services may be
331 those who have been in the host country for a longer time; they may differ from the general
332 population in terms of socio-demographic characteristics and, therefore, may have a
333 different risk profile for the infections. Moreover, no formal sample size calculation was
334 performed; some prevalence estimates on specific infections and subpopulations showed
335 a great uncertainty due to the small sample size of these groups.
336 Additionally, a selection bias cannot be ruled out. Enrolment in the study completely
337 relied on the staff dedicated to the project. It is likely that a proportion of patients eligible
338 for the study had been missed; however, they should not have been systematically
339 different from those enrolled because the physicians responsible for the enrolment
340 covered different care settings within their units. Moreover, not all the patients who were
341 asked to take part in the study gave their consent. The proportion of patients who did not
342 participate despite their eligibility was less than five percent in all the centres suggesting
343 that this source of bias is not substantial.

344 Another limitation of the study lies in the exclusive use of serology to estimate the
345 prevalence of selected NTDs in immigrants. As a matter of facts, these tests may not
346 distinguish between prior infection and active disease since antibodies may persist for
347 many months to years after successful treatment in most of the NTDs evaluated and these
348 tests are prone to cross-reactions with other parasite antigens [29]. Additional tests on
349 stool or urine samples would have certainly increased the diagnostic sensitivity but were
350 deemed not be feasible, given the logistic arrangement of the study that relied on a
351 centralised laboratory. Since the therapies for the infections under study are mostly short-
352 term and well-tolerated, we opted for treating all seropositive patients, except those
353 affected by *T. cruzi* infection, who underwent disease staging before treatment according
354 to current agreements [30].

355 Despite these limitations, our findings highlight the importance of tackling the NTDs
356 challenge in a non-endemic setting. The call for systematic detection and appropriate
357 management is even more urgent because it has been reported that health professionals
358 rarely consider these diseases. As a consequence, NTDs are highly likely to be
359 underdiagnosed at present, or diagnosed too late or inefficiently managed [31]. As
360 previously suggested in the European context, screening protocols seem to be a sensible
361 option [32]. A presumptive anthelmintic therapy for immigrants coming from areas at high
362 risk had been previously demonstrated to be cost effective in certain setting [27]. However,
363 this approach is not free from drawbacks, including toxicity, under-treatment of certain
364 infections [33] and risk of focusing on a single medical intervention while neglecting a
365 proper follow-up and a more comprehensive approach to migrants' health.

366 The importance of diagnosing and treating these infections is crucial among
367 immunosuppressed patients (for example those receiving chemotherapy, chronic steroid
368 or immunosuppressive treatment) and donors/recipients of solid organ and hematopoietic
369 stem cell transplantation, as well as blood transfusion [34]. Indeed, the rising success and

370 adoption of transplantation reasonably increases the proportion of the immigrant
371 population who will become donor/recipient of organ transplantation and
372 blood/hemoderivates in destination countries. Many of the pathogens that cause NTDs can
373 be either reactivated during immunosuppression or transmitted via organ graft or blood
374 transfusions [34], making a screening approach in these contexts life-saving.

375

376

377

378 We declare that we have no conflicts of interests.

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Infection	Numerator and denominator	Overall prevalence (95% CI)	Women to men ratio	Geosentinel Regions with highest prevalence		
				<i>Geosentinel Region</i>	<i>Numerator and denominator</i>	<i>Region-specific prevalence (95% CI)</i>
Strongyloidiasis	42/939	4.51% (3.35-6.05)	1:2	North East Asia	2/31	6.45% (1.48-23.93)
				Sub-Saharan Africa	20/330	6.06% (3.93-9.22)
				South Central Asia	5/90	5.55% (2.29-12.85)
Schistosomiasis	31/519	5.97% (4.22-8.37)	1:2.8	Sub-Saharan Africa	25/323	7.73% (5.27-11.22)
				South America	3/46	6.52% (2.02-19.05)
				South Central Asia	1/34	2.94% (0.37-19.77)
Chagas disease	7/180	3.88% (1.85-7.98)	2.5:1	South America*	7/172	4.06% (1.93-8.34)
Toxocariasis	11/113	9.73% (5.42-16.86)	1:1.8	South East Asia	2/6	33.33% (4.18-85.13)
				South America	4/19	21.05% (7.33-47.32)
				Eastern Europe	3/24	6.89% (3.73-34.48)
Filariasis	5/54	9.25% (7.83-11.63)	1:1.5	Sub-Saharan Africa*	5/34	14.70% (5.96-31.91)

* Only one region is reported because the infection was not found in people coming from other areas