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NEGLECTED TROPICAL DISEASES AND MIGRANTS: A GLOBAL HEALTH CHALLENGE AMID ACCESS BARRIERS AND LACK OF GOLD STANDARD DIAGNOSTICS

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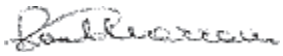
Signature 

NEGLECTED TROPICAL DISEASES AND MIGRANTS: A GLOBAL HEALTH CHALLENGE AMID ACCESS BARRIERS AND LACK OF GOLD STANDARD DIAGNOSTICS

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SOMMARIO

Questa tesi riguarda la salute dei migranti, con particolare attenzione alle malattie tropicali "neglette" (NTD) e ad altre infezioni, e si basa sull'esperienza di screening quotidiano e sul lavoro clinico svolto per diversi anni presso l'ambulatorio dell'Istituto Nazionale Migrazione e Povertà (INMP) di Roma, e sulla collaborazione scientifica con l'IRCCS Sacro Cuore Don Calabria per le Malattie Infettive e Tropicali e l'Università di Verona.

La tesi è strutturata in 5 capitoli principali, ognuno dei quali è composto da una breve introduzione e da uno o più articoli scientifici (6 articoli in totale).

Ogni capitolo si sviluppa a partire da una specifica domanda di ricerca.

Il capitolo 1 tratta delle barriere istituzionali e socioculturali che ostacolano l'accesso dei migranti al sistema sanitario nazionale, avendo come caso di studio l'approccio antropologico allo screening della malattia di Chagas nei migranti latinoamericani. Attraverso il caso di studio, viene indicato un approccio generale ai pazienti stranieri che tenga conto delle differenze culturali, sociali e linguistiche. Il capitolo 2 tratta dello screening delle malattie infettive in persone trascurate e "invisibili": minori e donne nigeriane vittime di tratta, affrontando anche questioni come le barriere di accesso alle cure per i migranti. Il primo lavoro, su un'ampia coorte, dimostra che i minori migranti sono generalmente sani e non rappresentano un rischio significativo per la popolazione autoctona. Il secondo lavoro mostra sorprendentemente che, nelle lavoratrici del sesso vittime di tratta, le NTD non trasmissibili, come la strongiloidosi e la schistosomiasi, sono molto più comuni delle malattie a trasmissione sessuale (MST) e dell'HIV. Il capitolo 3 descrive il processo che ha portato, attraverso un complesso lavoro interistituzionale in cui sono stata personalmente coinvolta, come membro del gruppo tecnico e del comitato di scrittura, alle prime linee guida nazionali in Italia per lo screening delle malattie infettive nei richiedenti asilo e nei rifugiati, che hanno aggiunto alle tradizionali infezioni trasmissibili due importanti NTD non trasmissibili, ovvero la strongiloidosi e la schistosomiasi. Il capitolo 4 descrive, attraverso il più grande studio prospettico mai condotto in Europa, la prevalenza delle due NTD e delle infezioni trasmissibili nei rifugiati e richiedenti asilo africani, rilevando un numero impressionante di persone affette da schistosomiasi urinaria e intestinale e (in misura minore) da strongiloidosi, e sottolinea la mancanza di un gold standard diagnostico per le due infezioni e la necessità di migliorare i test di screening. Il capitolo 5 tratta la valutazione di un nuovo test sierologico (non ancora disponibile in commercio) per la strongiloidosi, dimostrando una sensibilità e una specificità ragionevolmente buone. Sulla stessa linea, il capitolo 5 indica le linee di ricerca attuali e future per migliorare lo screening e la diagnosi della schistosomiasi.

Concludiamo che la gestione sanitaria dei migranti è estremamente complessa e impegnativa,

coinvolgendo allo stesso tempo scienza, etica, solidarietà, diritti, politica e determinanti della salute, diventando così una sfida sanitaria globale.

ABSTRACT

This thesis concerns the health of migrants, with particular attention to "neglected" tropical diseases (NTDs) and other infections, and is based on the experience of daily screening and clinical work carried out for several years at the outpatient clinic of the National Institute for Migration and Poverty (INMP) in Rome, and on scientific collaboration with the IRCCS Sacro Cuore Don Calabria for Infectious and Tropical Diseases and the University of Verona.

The thesis is structured in 5 main chapters, each of which consists of a short introduction and one or more scientific articles (6 articles in total).

Each chapter develops from a specific research question.

Chapter 1 deals with the institutional and socio-cultural barriers that hinder migrants' access to the national health system, having as a case study the anthropological approach to Chagas' disease screening in Latin American migrants. Through the case study, a general approach to foreign patients that takes into account cultural, social and linguistic differences is indicated.

Chapter 2 deals with infectious disease screening in neglected and 'invisible' persons: minors and trafficked Nigerian women, also addressing issues such as barriers to access to care for migrants. The first paper, on a large cohort, shows that migrant minors are generally healthy and do not pose a significant risk to the native population. The second work surprisingly shows that, in trafficked sex workers, non- communicable NTDs, such as strongyloidiasis and schistosomiasis, are much more common than sexually transmitted diseases (STDs) and HIV.

Chapter 3 describes the process that led, through complex inter-institutional work in which I was personally involved, as a member of the technical group and writing committee, to the first national guidelines in Italy for infectious disease screening in asylum seekers and refugees, which added two important non-communicable NTDs, namely strongyloidiasis and schistosomiasis, to the traditional communicable infections.

Chapter 4 describes, through the largest prospective study ever conducted in Europe, the prevalence of the two NTDs and transmissible infections in African refugees and asylum seekers, noting an impressive number of people with urinary and intestinal schistosomiasis and (to a lesser extent) strongyloidiasis, and emphasizes the lack of a diagnostic gold standard for the two infections and the need for improved screening tests.

Chapter 5 deals with the evaluation of a new serological test (not yet commercially available) for

strongyloidiasis, demonstrating reasonably good sensitivity and specificity. In the same line, chapter 5 goes on to indicate current and future lines of research to improve the screening and diagnosis of schistosomiasis.

We conclude that the healthcare management of migrants is extremely complex and challenging, involving at the same time science, ethics, solidarity, rights, politics and determinants of health, thus becoming a global health challenge.

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INTRODUCTION

Neglected tropical diseases (NTDs) are a heterogeneous group of conditions[1] that are mainly common in tropical countries (Africa, Asia, and Latin America) where many people do not have access to clean water or safe ways to dispose of human waste (1).

In fact, NTDs mostly affect impoverished communities causing devastating health, social and economic consequences to more than one billion people. The epidemiology of NTDs is complex and often related to environmental conditions.

Many of them are vector-borne, have animal reservoirs and are associated with complex life cycles.

NTDs are increasingly seen in non-endemic areas such as Italy where an increasing number of individuals affected by NTDs is observed, due to the increased migratory flux through the Mediterranean route during the last few years, especially from Sub-Saharan Africa, the substantial number of foreign-born residents and, to a lesser extent, the ever increasing number of travelers (2- 4).

The real burden of NTDs in Italy is unknown and available data are likely to underestimate the real prevalence, also because most of NTDs do not require hospitalization, most cases, especially in illegal migrants, remain undiagnosed and the surveillance system of the Italian Ministry of Health establishes that only some of the NTDs must be reported.

Morever, in the published studies the diagnostic tests used were not homogenous.

Although some NTDs are endemic both in Italy and in other countries, in most cases (such as strongyloidiasis and schistosomiasis) it is easy to establish that the disease was contracted in the country of origin, as for both of them the risk of transmission in Italy is virtually null.

The Italian Society of Tropical Medicine and Global Health (SIMET) promoted a survey (5) in nine Italian sentinel centers to investigate the occurrence of some more frequent NTDs such as schistosomiasis, strongyloidiasis, cystic echinococcosis, Chagas disease, leishmaniasis, cysticercosis, filariasis and scabies, in order to identify for which diseases public health interventions, development of standardized protocols for case management and training activities should be prioritized.

The survey also draws attention to the diagnostic and therapeutic difficulties of many NTDs in Italy and also to the lack of knowledge of these diseases by health care professionals, leading to diagnostic delay and case mismanagement.

Concerning diagnosis, reliable tests are only available only in a few tertiary care centers, thus the

[1] NTDs include: Buruli ulcer, Chagas disease, dengue and chikungunya, dracunculiasis (Guinea-worm disease), echinococcosis, foodborne trematodiases, human African trypanosomiasis (sleeping sickness), leishmaniasis, leprosy (Hansen's disease), lymphatic filariasis, mycetoma, chromoblastomycosis and other deep mycoses, onchocerciasis (river blindness), rabies, scabies and other ectoparasitoses, schistosomiasis, soil-transmitted helminthiases, snakebite envenoming, taeniasis/cysticercosis, trachoma, and yaws and other endemic treponematoses

diagnosis of such conditions is often delayed or missed, resulting in excess, avoidable morbidity, while access to treatment is affected by a number of bureaucratic and economic obstacles and low interest of the pharmaceutical industry and policy makers. Praziquantel, the drug of choice for schistosomiasis, is not registered for human use and the price for importation may vary between centers, based on the agreement between single hospitals and the authorized importers; ivermectine, the only effective drug for strongyloidiasis, has only recently been registered in Italy and can be found in Italian pharmacies as a "Class C" drug, at a prohibitive cost for most migrants. The survey also showed that schistosomiasis and strongyloidiasis are the most common NTDs diagnosed in Italy with a prevalence of 4.5 and 6% respectively (6).

The authors note that applying these prevalence figures to the about 1 000 000 African subjects who are currently regularly residing in Italy, it is estimated that 45 000 and 60 000 people are potentially infected with *Strongyloides stercoralis* (*S. stercoralis*) and *Schistosoma* spp.

Other studies reported a higher prevalence of these neglected parasitic infections; a prevalence study published in 2018 showed that out of more than 300 migrants from Sub-Saharan Africa, 21% were affected by schistosomiasis with peaks of 70% for those from Mali, and about 18% were affected by strongyloidiasis.

Strongyloidiasis or schistosomiasis are not dangerous for the autochthonous population, as because of person-to-person transmission does not occur, but both can cause serious health consequences for infected individuals., even after many years. *S. stercoralis* can cause disseminated infections with fatal outcomes in immunosuppressed patients and schistosomiasis is the result of an immune-mediated granulomatous response to trapped eggs that produces organ-specific manifestations, causing chronic hepato-intestinal and/or urogenital severe complications.

Different studies have estimated the prevalence of a number of communicable and non-communicable infectious diseases in migrants recently arrived in Europe, showing, for instance, that in individuals from sub-Saharan Africa the non communicable helminth infections are far more common than the communicable sexually transmitted infections and TB. Despite scientific evidence, human mobility has long been associated with the spread of infectious diseases, and the message that constantly passes through public opinion is that migrants fleeing from precarious situations are associated with the introduction of infectious pathogens into their host countries, thus being perceived as a biological threat that must be "cleaned up".

On the contrary, several studies have shown that infectious diseases are not the main problem affecting migrants. Mental conditions, including depression and anxiety disorders, as well as the consequences of physical traumatism, violence and torture, are probably the first health priorities in this population.

Moreover, clinicians should be careful not to fall into the “Salgari syndrome” that is the predisposition of health workers to look for exotic diseases in immigrants at all costs, based on the preconception that coming from another country (especially a tropical or subtropical one) invariably corresponds to being carriers of unusual conditions. The syndrome is named after Emilio Salgari, the renowned 19th century Veronese novelist, who was gifted with a vivid imagination and aptitude for describing unreal scenarios, setting his stories in remote areas, even though he had never been there.

In reality, immigrants often belong the strongest and most motivated part of their native country population (the so called “healthy migrant effect”). However, the discontinuous life paths, the detachment from one's own culture and from the known social context, the absence of protection from the family unit, the difficulties in adapting to the new environment, the compromised nutritional status and the climate of socio-economic deprivation, represent aspects that over the years have contributed to a significant worsening of the individual's psycho-physical well-being, thus causing the so-called “exhausted migrant effect”. The latter is certainly predominating in the majority of asylum seekers in recent years, fleeing from wars and famine and gradually replacing the “economic migrants” of the previous decades.

Therefore, it should be emphasised that infectious diseases among migrant populations, including those that are communicable, largely reflect poor living conditions and social marginalisation, and are therefore likely to remain confined to their communities without spreading to native people.

However, even if newly arrived migrants are mostly healthy, they can harbor latent infections that can remain undiagnosed long after migration and need appropritate screening policies and careful surveillance, also also in order to prevent the potential (re)introduction of infections and vectors.

The migrant health care is complex and influenced by pre-migration circumstances, the impact of migration journey and time to resettlement, and the social determinants of health related to their post migration situation.

Screening programmes for major infectious conditions should be systematically implemented and adapted to the different stages of the migration process. In addiction to epidemiology of infectious diseases in the countries of origin, the circumstances of how and why persons migrate may increase the risk of exposure to crowded living conditions, violence and transmission of infection throught direct contact, blood and airborne routes.

Moreover, adequate medical preparation is necessary; diseases such as leprosy, schistosomiasis, strongyloidiasis or other tropical diseases are in fact difficult to manage if not recognised through proper knowledge of the geographical epidemiology.

Additionally, facilitating the orientation of affected persons towards the appropriate diagnostic and treatment pathways, ensuring that they are taken care of and avoiding stigmatisation, would make it

possible to circumscribe possible infectious outbreaks, to the benefit of everyone's health.

The interest in knowing the diseases or rather the health profile of immigrants should not fuel prejudices or fears, but rather should convince that ensuring the health of this population is achieved through inclusion in the 'national health system' by fostering access to and use of health services.

This clinical-epidemiological thesis with a predominantly translational character aim to address the issue of the screening of infectious pathologies in the migrant population with particular regard to neglected tropical diseases.

This thesis will attempt to address in a scientific manner and from a global health perspective the multiple aspects that the complexity of the healthcare reception of this population involves.

MAIN RESEARCH QUESTIONS

1. How to improve migrants' access to health care using a socio-culturally and linguistically-appropriate approach?
2. Which infectious diseases affect the most vulnerable and neglected migrant populations (namely, unaccompanied minors and female sex workers)?
3. Are there evidence-based recommendations on health assessments for migrants and asylum seekers upon their arrival in Italy?
4. How can the true burden of Neglected Tropical Diseases (NTD) be assessed in refugees and asylum seekers from Africa, in the absence of a diagnostic gold standard?
5. Can the diagnosis of the two major NTDs, strongyloidiasis and schistosomiasis, be improved by the introduction of new tests?

CHAPTER 1 – INSTITUTIONAL AND SOCIO-CULTURAL BARRIERS TO MIGRANTS' ACCESS TO THE NATIONAL HEALTH SERVICE

In order to implement the appropriate screening activities for migrants and to ensure adequate access and contribute to improve trust in public health services, it is necessary to consider a few, main barriers to access, often related to immigration concerns among undocumented immigrants, health legislation, institutional health service characteristics and linguistic, economic, social and cultural issues.

In the article "Anthropological study on Chagas Disease: Sociocultural construction of illness and embodiment of health barriers in Bolivian migrants in Rome, Italy", we used both ethnographic and biomedical methods, to study Chagas disease, a neglected tropical disease endemic in many Latin-American countries.

Anthropological involvement, in the approach to the illness of the migrant patient, ensures that some account is taken of local knowledge, cultural influence on the patterns of disease, and structural barriers to good health.

Working with a medical anthropologist meant recognising the complex relationship between culture and health. This relationship consists in understanding that culture is made up of beliefs, practices and moral, political, economic, legal and ethical principles that in different societies, and even within the same society, are aimed at achieving individual and community health and well-being. According to the Lancet's Culture and Health Commission, 2014 (6) "systematically neglecting cultural issues in health care is a tendency that alone represents the greatest obstacle to improving health standards in the world".

Caring for migrant people inevitably involves a strong focus on socio-cultural diversity, the historical, economic, social and cultural aspects that contribute to the construction and expression and representation of illness and suffering.

In the article we analysed the institutional, economic and legal barriers, the sociocultural construction of the diseases, the barriers, such as illness-related stigma, to access the National Health Service (NHS) for those potentially affected.

The results of the study were important on the one hand to understand how to reach such a complex and diffident target group, so unaccustomed to accessing the NHS, how to overcome heterogeneous barriers and act on such relevant diagnosis and treatment pathways, and on the other hand, the research was also able to directly impact on the health care provision, not only for Latin American immigrants. Working times and timetables were modified several times, adapting to the people and their needs; language barriers were overcome, at least partially; a specialised team was set up to take

care of the numerous aspects brought by the study's target persons, not only those directly related to health.

PLOS ONE

RESEARCH ARTICLE

Anthropological study on Chagas Disease: Sociocultural construction of illness and embodiment of health barriers in Bolivian migrants in Rome, Italy

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Abstract

Introduction

Chagas Disease (CD) is endemic in many Latin-American countries, Bolivia in particular. It is now spreading in Italy as a host country for transcontinental migrants and becoming an emerging health problem. This anthropological action–research, as part of a wider medical project on Neglected Tropical Diseases, has the purpose of analyzing the sociocultural construction of CD and its representation in Bolivian people living in Rome as well as barriers, such as the stigma about the illness, to access the National Health Service for those potentially affected.

Methods

The ethnographic study was carried out from 2016 to 2018 by a medical anthropologist at the National Institute for Health, Migration and Poverty (INMP) on 72 Bolivian migrants (47 women and 25 men) living in Rome. The study was carried out through: a territorial mapping of Bolivian networks and communities aimed at recruiting people, participant observation, and application of semi-structured and unstructured interviews. The interviews were hold in Spanish and proposed to all participants before or during medical examination, or during events organized by the Bolivian community in Rome. The interview consisted of 16 items and covered four macro areas: personal and migration history, health status, access to the Italian National Health Service and knowledge about CD; plus 5 items for those who received a diagnosis of Chagas Disease in Italy.

funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: The authors have declared that no competing interests exist.

Results

The sociocultural construction and the deep stigma about the illness built by participants and their families could hinder both diagnosis and treatment. Institutional barriers also contributed to reduce adherence to screening tests: often, opening hours of the outpatient clinic were incompatible with participants' precarious employments. To guarantee participant's access to public health services and their adherence to the diagnostic protocol, we implemented a profound revision of our cultural and institutional approach to them.

Conclusions

The analysis evidenced the limitations of the conventional approach applied by the Italian National Health Service to this migrant community, such as the absence of socio-cultural and linguistics competences that can help understanding patients' perception and representation of the illness. The multidisciplinary approach instead—with clinicians using the ethnographic results to adjust their work to the participants' needs—was a successful attempt to ensure therapeutic alliance.

Introduction

Chagas Disease (CD) is one of the so-called Neglected Tropical Diseases (NTDs), mainly rooted in rural areas of the del American continent and spread through internal and external migration [1, 2]. NTDs affect populations living in poverty, without adequate sanitation and access to clean water or proper ways to dispose of human waste and in close contact with infectious vectors, domestic animals and livestock [1]. CD seems to be a metaphor for those social inequalities and poverty conditions that are produced in the contexts of origin and later reproduced in the migratory hosting countries: therefore, it is possible to state that CD can be eligible to receive a sort of archeological analysis.

CD has now become a global health phenomenon affecting a significant number of people, also in non-endemic countries—particularly southern European countries such as Spain and Italy [3–7]–where it is generally hardly diagnosed and therefore underestimated [6–9]. Chagas spread in Europe and mainly in Italy occurs through different non-vectorial routes. It is due to population movements, blood transfusion or organ transplant, childbirth, adoptees people visiting friends and relatives and, also, by laboratory-accident transmission. It is common for European doctors to have little or no experience with the detection and management of Chagas disease [7]. Mainly because of the difficulty of migrants to access screening and prevention programs, and because CD is not included in traditional diagnostic-therapeutic pathways [7]. This disease, however, can be reactivated in immunosuppressed patients, giving rise to serious and potentially fatal clinical pictures [4–6].

Although epidemiologic data about CD presence in Italy are very limited, approximately 6–12,000 estimated cases [10–12], the highest prevalence is estimated among migrants from Bolivia [4].

The triatomine bug usually called *vinchuga* or *chinche* by the inhabitants of Latin America is the main vehicle for the protozoan parasite *Trypanosoma Cruzi* (T. *Cruzi)* that ultimately causes Chagas Disease. Vinchuga is widely spread in Latin America, especially in rural areas (other typical names are *chipo*, *pito*, *barbeiro*, *chichaguaz*). In both endemic and non-endemic countries, inter-human transmission of *CD* can also occur by means of blood transfusion and

tissue transplantation, or congenitally from mother to child [13–15]. Once infected, it is possible to be asymptomatic for years before showing heterogeneous symptoms involving cardiac, gastrointestinal and central nervous system [2, 16].

The World Health Organization (WHO) estimates that about 6,000,000 people are infected by *T*. *Cruzi* throughout the world, 62% of whom live in countries of the Southern Cone, Bolivia in particular, where at least 6% of its population is considered affected [17, 18]. In 1999, Bolivia launched the Chagas National Program ("*Programa Nacional de Chagas*" in Spanish) trying, in this way, to sanitize all the endemic municipalities of the country; finally, in 2006 the eradication was qualified as a national priority with Bolivia's Chagas Disease Law [19]. To fulfill the purpose, the government offered free diagnosis and treatment in all major cities but without considering the individual and collective sociocultural construction about CD and the etiological and therapeutic "traditional" system based on other knowledge and care systems—the so-called imaginary about Chagas and its vectors in the target population [20–24]. These aspects would have been of great importance for the implementation of health campaigns in terms of prevention and sustainability [25–27] but unfortunately, they were not considered.

Starting from this historical and epidemiological framework, we launched our anthropological research on CD as a part of a project on NTDs: "Strengthening the fight against neglected Tropical Diseases in the migrant population through the use of medical devices", precisely in consideration of the above-mentioned social and cultural aspects, but also of the political and social contexts from which immigrants come—pervaded by the violence of poverty—that strongly affect the Chagas diagnosis and treatment also in Italy [28, 29]. The challenge of this research, was to keep together the migratory process from the native land to the host country —that also determined the conditions of poverty in Italy—with the Chagas concept that the research target people had of the disease. This by trying not to reduce the disease only to its biophysical dimension [30], but including in the clinical action the perspective of the patient, the one who experiences the disease, who incorporates and represents it [31].

Research objectives

The main research objectives are: i) to investigate the occurrence of Chagas disease among Bolivian migrants living in Rome; ii) to analyze the socio-cultural disease construction processes and its representation in relation to the migratory condition; iii) to disclose the social impact of the disease; iv) to identify the barriers to access Italian public health services for potentially affected people.

The INMP anthropologist and the infectious disease specialist used both ethnographic and biomedical methods, by sharing and combining them. To achieve the above-mentioned objectives, the steps taken were the following: a) data collection about existing health policies, both in the country of origin as well as in Italy; b) analysis of the correlation between CD and socio-economic conditions, migration status and institutions; c) analysis of the social and political causes of CD production (and reproduction), both in the country of origin as well as in Italy, d) investigation of the collective imaginary about CD.

Study context

Anthropological research is part of the clinical project "Strengthening the fight against Neglected Tropical Diseases in the migrant population through the use of medical devices", whose general objective to strengthen the fight against NTDs in migrant population from endemic areas living in Rome, through: (i) an estimate of the spread and epidemiological characteristics of some major neglected tropical diseases such as strongyloides and other geohelminthiasis, schistosomiasis, and Chagas disease; (ii) the early identification and early care of

affected migrants. The anthropological study, that only focused on CD, was built to contribute to study the processes of spread of neglected diseases, their understanding and explanation, through theoretical-methodological tools. Final aim is to implement local health policies able to combat these diseases, primarily considering them as a social and economic problem, then a political and legal issue and, at last, a health concern. What we report in this work is the transcultural and transdisciplinary approach usually adopted at the INMP when providing health care to specific populations (poor and disadvantaged groups, regularly and irregularly staying foreigners, victims of violence and trade, international protection applicants).

The anthropologist recruited Bolivian patients for the project and interviewed them for the purpose of research; she followed them throughout the whole medical path to establish a relationship based on trust: during the first medical examination when blood tests were prescribed; when these tests were carried out; in the course of other examinations when the diagnosis was communicated. Then if Chagas diagnosis was positive, she contacted the patients and their families by phone during the whole period of hospitalization in which they were subject to instrumental diagnostic tests and CD treatment.

Methods

Study design

The ethnographic study was carried out by the medical anthropologist from August 2016 to July 2018. It included participant observation and administration of both semi-structured and unstructured interviews. All communications and interviews were conducted by the first author in Spanish.

In the first phase of the project—that lasted about one year—we mapped the Roman territorial network to detect Bolivian migrants for possible enrolment in the project. In the second phase we contacted the identified people and associations by telephone or e-mail and offered them free enrollment in the clinical project as well as in the anthropological research. In case of a positive answer, we scheduled an appointment at our outpatient clinic.

Sample

Eligibility criteria for the sampling required: from 18 years old, to be born and have lived in Bolivia before migrating to Italy, not having a previous diagnosis of Chagas. After signing an informed consent, 72 undiagnosed Bolivian migrants living in Rome were recruited by the first author from December 2017 to June 2018 at the outpatient department of National Institute for health, Migrant and Poverty (INMP), in Rome, Italy.

Procedure: Participant observation and interview

The ethnographic interviews were conducted in fluent Spanish by the first author at the outpatient clinic, whether during the first medical examination or at the communication of the laboratory tests results. The anthropological activity also included participant observation of the relationships between the doctor and the participant or between the doctor and the family members, for example during medical examinations. Furthermore, participant the observation was rigorously applied during each meeting with the participants, and data reported immediately on a notebook. Additional interviews were administered to participants met during events organized by the Bolivian community in Rome (parties, carnival parades and sport games) or at the housing occupations (squats) where some of the participants lived. Interviews (consisting of 21 items) were semi-structured and unstructured, and guided by a list of topic question (e.g. "By what or who can Chagas be caused?"—Investigate magical-religious, socio-

cultural, socio-economic aspects -; "What do people you know think about Chagas?"—Investigate aspects of the social and family imaginary; prejudice, possible isolation, contagion -;—If Chagas diseases is diagnosed- "Since you have this disease, how has your life changed?"; "Did you or your family members ever visit the doctor because of Chagas Disease in your country and in Italy?—Analyze costs and social stigma).

Sometimes the topics changed as the formulation of the meaning of illness developed. The interviews lasted about 30–40 minutes, written down directly and no audiotaped. They covered four macro areas: i) personal history; ii) migration history; iii) health status and access to the Italian National Health Service; iv) prevalent knowledge about CD.

Conversation was never forced, to respect feelings and emotions as well as to provide the time needed by each person or family member. Furthermore, before starting the interview, people were asked what language they preferred between Italian or Spanish.

All the interview items are detailed in Table 1.

Data analysis

The interviews were directly transcribed in Spanish, organized and printed for content analysis; field notes written in Spanish on notebooks were analyzed. Content analysis was conducted from September 2018 to January 2019 manually, through the process of *coding* [32, 33], without using any content analysis software.

Table 1. Items included in the anthropological interview.

Life history	Personal data
	Education
	Marital status
	Employment and socio-economic status in the country of origin
	Current job (contract type, salary, treatment by employers)
	Living condition in Italy and type of accommodation
Migration history	Date of arrival in Italy
	Migratory reasons
	Migration experience and legal status in Italy
Health status and access to the Italian National Health Service	Perception of the health status
	Access to Italian hospitals
	Access to family doctor
	Health barriers
	Family health history
Chagas Disease	Knowledge about the disease
	Personal experience
	Imaginary
	Previous analysis for Chagas disease
	Disease as a perceived stigma in both Bolivia and Italy

We interviewed each participants at least once, a second interview was administered in case of positive diagnosis of CD. In some cases, we had to administer interviews in a fragmented manner (i.e. in the waiting room—when the patient was alone -, or, in presence of the doctor, before, during or after the clinical examination and even during blood tests) because of the regularly short time available for participants to stay at our clinic due to work reasons.

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Ethical statement

This anthropological study is part of the Tropical Neglected Diseases Project: "Strengthening the fight against neglected Tropical Diseases in the migrant population through the use of medical devices". It was led by the Italian National Institute for Health, Migration and Poverty (INMP) in Rome and approved by the Ethical committee of the Italian Higher Istitute of Health (Istituto Superiore di Sanità—PRE-712/16).

All people involved in the study signed a written consent according to the Declaration of Helsinki [34].

Results

Territorial mapping of Bolivian population living in Rome

Out of the number of organizations, associations and institutions contacted, the following are those who responded positively, sending to their Bolivian contacts the proposal to participate in the research. The reached local network was wide and included many people: the Bolivian Embassy, the roman Bolivian community of the "Asociación de la Comunidad Boliviana", the roman Bolivian community (not belonging to the "Asociación de la Comunidad Boliviana"), other Latin American associations, Italian schools for foreigners, centers for adopted children, Latin American Christian centers in Rome, parishes, nunneries as well as the Latin American Anglican Church, Catholic communities and self—managed housing occupations.

Territorial mapping played an important role in identifying a larger number of Bolivian migrants for enrollment and facilitating their access to our outpatient clinic for CD screening.

Participants' data

No drop out was registered, all the people who were asked agreed to be interviewed. We interviewed 72 Bolivian migrants, 47 women (65.3%) and 25 men (34.7%), mainly from the municipalities of Cochabamba, Oruro, Santa Cruz and La Paz, located in central Bolivia. The large presence of women in the research shows the feminization of migration, typical of Latin America, which is also widely analyzed in literature [35–37].

Participants' age ranged from 16 to over 65 years old (median age 43.3) (Table 2); most people had a medium-high education: 49 people (68.1%) had a high school diploma: 7 of them (9.7%) had a degree, of which 5 were women (6.9%).

Interview administration

The anthropologist had a leading role in recruiting participants both for clinical screening and for the interview. Though the duration of interview administration was between 30 and 40 minutes (mean duration of 35 minutes), few participants agreed to participate in a larger number of encounters aimed at deepening socio-cultural aspects related to the disease. In many cases, the impossibility for participants to stay at our outpatient clinic for the needed time led to a fragmentation of the interviews into multiple encounters.

Immigration, work and access to healthcare

Bolivians are quite a stable population in Rome: 97.4% of the interviewed had a residence permit and, among them, 48 (66.7%) had lived in Italy for more than 10 years and had a full (33 people– 45.8%) or part time job (17 people– 23.6%) (Table 2).

Migratory projects have multiple roots and result from individual choices as well as from contextual conditions concerning both the attraction for the immigration country and the reasons for leaving the country of origin [38–40]. Below, we analyze women more than men not

Table 2. Distribution of selected characteristics for participants in anthropological study on Chagas Disease 2016–2018.

Age	N°	%
16–17	3	4.2
18–34	9	12.5
35–54	50	69.4
55–64	8	11.1
Over 65	2	2.8
Sex		
F	47	65.3
M	25	34.7
Marital Status		
Married/cohabitee	42	58.3
Unmarried	22	30.6
Widow	2	2.8
Separated/divorced	6	8.3
Qualification		
Junior high school diploma	16	22.2
High school diploma	49	68.1
Degree and beyond	7	9.7
Employments		
Part time job	17	23.6
Occasional job	3	4.2
Housewife	4	5.6
In search for a new job	9	12.5
Full time job	33	45.8
In search for the first job	1	1.4
No answer	5	6.9
Works performed		
Caregiver for elderly/ baby sitter	18	25.0
Domestic helper	23	31.9
Clerk	2	2.8
Unspecified employment	5	6.9
Industrial worker	2	2.8
Construction worker	2	2.8
Teacher/educator	1	1.4
No answer	19	26.4

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only because they are more numerous, but also because Bolivian immigration, such as that of other Latin Americans in Italy, is predominantly female. Furthermore, they also are the ones who take care of the whole family remaining in the country of origin, until the possible family reunification in Italy. It is also important to contact and establish a good relationship with them because of the risk of mother-to-child transmission [13–15]. This scenario is undoubtedly a major public health problem, since affected people may ignore CD signs and symptoms and become seriously ill, and even die, without ever receiving a CD diagnosis. Most Bolivian women migrated to Italy alone: in most cases, they followed a female protective network of sisters, cousins and aunts who previously arrived. Conjugal reunification normally occurs after many years. It is interesting to note that 58.3% of the interviewed are married and only 8.3% separated or divorced (Table 2); however, due to the difficulties of separation/divorce, a

substantial number of women created new relationships, exclusively with Latin American men, without formally interrupting the previous bonds.

Many of the interviewees lived with their family and friends in rented or subleased houses or in abandoned buildings (Housing Squat) irregularly occupied and managed by urban social movements.

In their country, Bolivian women had employments consistent with their qualification and professional skills; this is why their migratory project is built upon the hope of improving economic income, to help their family and children with a possible employment inherent to their studies. Despite the high educational level, almost half of the Bolivian women in Rome are employed as domestic helper (23 people, 31.9%), babysitters or caregivers for elderly (18 people, 25.0%) (Table 2).

In the domestic and elderly care work field, it is possible to identify intensive processes in the formation of ethnic niches. Common feelings are those of frustration and resignation, due to the awareness that "as migrants" they can only access to a certain range of unskilled and poorly paid employments. Often, they are subjected to violent forms of domestic slavery, preventing them even from being absent for medical examinations, despite their regular contractual condition. Below the illustrative testimonies of two women:

> I used to work as a maid, then I had cervical problems and had to quit. Now I work with two kids, but not every day. I always have had a job by the hour. These jobs are the only ones we can do here
>
> (Marta—May 7, 2018).

> In Bolivia I used to work with an NGO in the schooling of women and poor people, here I work as caregiver of two elderly people who have Alzheimer's. . . and they are also aggressive, I am practically a slave. They never let me go out; I have little time only on Sundays to come for the analysis and the visit. I am here to work, because I have to help my children who are graduating in Bolivia, that is why I do not give up
>
> (Luz—July 8, 2018).

Social and cultural construction of Chagas Disease: Fear and stigma of poverty

Among the 72 participants interviewed, screening procedures revealed 22 adults (30.5%)– 18 women and 3 men—positive to CD: later, they were hospitalized for disease staging and treatment. All the participants affected by CD came from the Departments of Santa Cruz and Cochabamba, the Bolivian areas in which the disease is more widespread [19, 20, 41]. Communicating screening results generated a profound feeling of shame in the affected participants.

As said, the stigma associated with the disease clearly appeared during diagnosis communication and during or after hospitalization, thus making the disease as permeated by a deep stigma. The following narratives are very illustrative:

> Having Chagas, means being born in the country, in poor houses, because only in poor houses *vinchuca* can live
>
> (Alfredo—March 3, 2018).

Table 3. Distribution of patients included in anthropological study on Chagas Disease 2016–2018 on the basis of their permanence in Italy.

Year of arrival in Italy	N°	%
0 to 2 years ago (2018–2017)	4	5.6
3 to 5 years ago (2016–2014)	2	2.8
6 to 9 years ago (2013–2010)	8	11.1
10 to 20 years ago	48	66.7
More than 20 years ago (Before 1999)	4	5.5
No answer	6	8.3

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> I come from a very poor background, I lived in the countryside, I was used to sleep on the ground, on banana leaves and I had no "light" at home. When we lit up the torch at night we used to see all the *vinchucas* walking on the walls, they were full of blood and surely they had stung the whole family. I cannot believe I lived like that, but now I am in Italy and I don't want to think about it anymore
>
> (Roland—March 8, 2018).

> I do house cleaning, but how do I get to the hospital? My employers are very particular, as soon as they see that I have a cold they will not let me back in the house because they say that I am infected
>
> (Carlita—April 29, 2018).

Barriers to health: The weight of the Italian language, its culture and its health services

Despite many years spent in Italy (Table 3), the use of the Italian language by the interviewees was limited to the basic "technical" communication related to daily work activities.

Interpersonal relationships are limited to other members of the local Bolivian community, family members residing in Bolivia and in other European countries. Out of these contexts, interaction is minimal, even when necessary to exercise one's rights, including health rights. Indeed, most of the interviewed people had a health card expired for years and did not know how to access the National Health Service; in the event of acute situations they just referred to the territorial emergency rooms.

In this scenario, it is understandable the skepticism that people showed when they were offered a free health screening to look for a disease and more, in the absence of symptoms. While the medical doctor insisted for prevention, this precise concept was causing suspicion in the recruited participants: a health intervention causing inability to work for one or more days was useless, especially in the absence of pain. Moreover, screening given freely accentuated their suspiciousness thus raising doubts of being "used" for scientific purposes instead of representing a reassuring element. Overall, this diffidence has accompanied all the research phases, including the moment of signing the informed consent, which often required extensive explanation by both the medical doctor and the anthropologist.

Discussion

Our findings show that strengthening the fight against Chagas disease in Italy is no longer just a biomedical act. To intervene on the disease at a diagnostic and treatment level, we observed

how decisive it was to consider aspects such as: fragile socio-economic conditions, difficult access to the Italian National Health Service due to linguistic, economic and legal barriers and precarious working conditions that makes it difficult to undergo a medical examination, and even more problematic to leave the workplace for hospitalization in case of administration of Chagas Disease treatment. Moreover, we also observed how the "explanatory models" of *illness* (perception of suffering according to the patient)—which revealed the stigma of poverty as a deterrent to treatment—and of *disease* (interpretation of suffering according to biomedicine) [30] have significantly interfered with the possibility of healing and curing [42].

The territorial dislocation of the stigma

The dichotomous nature of Chagas and its various implications—ecological, social, political, economic and legislative—are the reasons why CD appears full of ambiguity and complexity. Furthermore, its predominantly asymptomatic character raises its invisibility whereas it does not weaken the deep stigma it is permeated by. To this regard, during the study, it appeared clear that all the participants tried to forget the disease and leave it in the shadows to hide the poor contexts of origin where they could have potentially become infected. The health care project of which the ethnographic study is part recalled the risk of the disease among people who live in Italy and, for these reasons, it inspired many contrasting feelings and attitudes that found their evidence in both recruitment and compliance difficulties that were observed and described (for example, the project was normally positively welcomed but then laboratory tests and subsequent appointments were often escaped).

In this context, the anthropological research pointed out the implicit unsaid about Chagas Disease and the stigma's semantic codes that were causing poor compliance. This latter aspect clearly emerged during the research and had a strong impact on the completeness of the collected data. Haste and anxiety were common feelings during the procedure to access our outpatient clinic. Some participants, once arrived in the waiting room, leaved the Centre because it was impossible to wait 30 minutes to complete registration before meeting us. The fear of losing their job and the specter of not being able anymore to send economic remittances to their families became an important health barrier. For all of them, the anthropologist had to contact and plan easy and individualized accesses during non- working hours, including Saturday and Sundays. This entailed a complex negotiation, positively resolved, of socio-cultural and biomedical codes between participants and medical doctor/anthropologist.

Additionally, the above-described fear of losing their job also had a major impact on that related to receiving the diagnosis. We faced several difficulties in planning the appointment to communicate the results of laboratory tests, since a positive result could mean having to deal with other encounters to be scheduled for supplementary diagnostic tests, therapy and follow-ups.

Cultural metaphors of poverty

Having Chagas means being born in the countryside, in poor houses, because *vinchuca* can live only in poor houses. Participants here hide their past living conditions, not only to the other members of the Bolivian community but, frequently, also to their own relatives. In this sense, it was extremely important for those diagnosed with CD (and their families) to secrete hospitalization from their compatriots, though sometimes this could have been difficult to achieve especially for those who lived with other Bolivians in the same housing occupation. In this regard, it is useful to know that the occupied buildings that hosted many members of the Bolivian community do not always have single apartments for each family, but functional

spaces shared by several families, with one bathroom available for numerous people and a high level of proximity and promiscuity. The impossibility to hide one's absence or a family member's for the entire duration of the hospitalization, represented a profound resistance to treatment.

At the same time, we started to observe frequent alliances and conflicts, rising within and between communities both during interviews and social events: in most cases, participants used to mutually blame for having built up a false and fictitious social status, claiming—for example—to have grown up in a "city context" while real origins were to be found in the countryside and its poor environment. Having CD actually reminded participants of their precarious conditions as well as the poor context they came and from which they had escaped in the hope of rebuilding a new identity in a completely new reality, even if under the unsatisfactory condition of underemployed migrants.

According to this, we can undoubtedly say that Chagas disease threatened the construction of a self that was socially functional before, but which seems now to hold hostage the possibility of cure.

The need for hospitalization of positive participants had also a more practical, not less important consequence, related to the risk of losing the job. On one hand, the impossibility to stay away from work for a few days (most women are engaged in the care of the elderly and children); on the other, the fear of stigma by the employers too (if they do not know Chagas disease they may think it is a contagious pathology able to be transmitted to their family members as well).

Issues of multidisciplinary approach

Our findings showed us that in our contemporary societies, crossed by such massive migration flows, the construction of multidisciplinary care spaces in public health, able to integrate the knowledge of social sciences—in particular medical anthropology—with that of biomedicine, is a health strategy that reveals benefits both for migrants and the host society. Indeed, the lack of familiarity with the categories of "illness" and "disease", which are characteristic of a particular system of thought, and other etiological and therapeutic registers, are at the origin of many of the difficulties reported by health care professionals.

In our study, the effects of anthropological research were intended to aimed at directly intervening in the clinical project. Based on the results obtained, in fact, hours and days of medical examinations were modified, thus causing a structural intervention in a public health structure. Therefore, communication between doctor and patient was modified if hospitalization was provided, favoring the emergence of individual and familiar resistance to treatment due to the social consequences (especially when cohabitation made it explicit) of being affected by Chagas, therefore poor people from Bolivian rural areas. Additionally, all interviews, conversations and communications were in Spanish: the use of the native language was another key piece of the overall framework, since it gave staff members more chances to investigate and gather effective and additional evidence of how participants do experience Chagas illness [43].

During this research-action, clinicians and anthropologists succeeded in holding together both the clinical and ethnographic methods, thus applying what the ethnopsychiatrist Georges Devereux used to call "the double discourse". By this label, it is meant clinician's and participant's discourse [44], which are now considered as complementary items in all existing care practices.

Limitations

Our study has several limitations. Firstly, only 72 participants were enrolled. From the beginning of the research, we found serious difficulties in recruiting participants due to several factors: precarious working conditions prevented them from taking appointments and keeping them; important stigma affecting Chagas disease in the communities of origin and in Bolivian communities in Rome. In this case, it was complex to maintain a continuous relationship with people who did not want to be hospitalized when necessary and for a period of time avoided any contact, even by telephone, skipping the appointments both with the anthropologist and the doctor.

Secondly, the anthropologist recruited the patients in Bolivian roman community for the clinical project on neglected diseases before and, after that, for the ethnographic research. This procedure, on the one hand facilitated project activities, because participants were at the outpatient clinic to be to be taken care of, but, on the other hand, the study was affected by patients' difficulties with Chagas' disease and the treatment paths related to it.

Finally, the anthropologist translated from Italian to Spanish and *vice versa* also during medical examinations and laboratory tests. This aspect certainly facilitated interview administration. However, this also probably created the conditions under which the participant-patient hardly would have escaped such a request.

Supporting information

S1 Interview. Semi-structured and unstructured interview in English.
(DOC)

S2 Interview. Semi-structured and unstructured interview in Italian.
(DOC)

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CHAPTER 2 – INFECTIOUS DISEASE SCREENING IN NEGLECTED AND "INVISIBLE" PATIENTS: UNACCOMPANIED REFUGEE MINORS AND FEMALE SEX WORKERS

Over the last few years, the global population of unaccompanied refugee children and adolescents who migrate without their legal guardians is increasing and mainly come from countries where there is armed conflict and oppression, or human rights abuses. Many studies have shown that asylum-seeking children and adolescents are at risk of developing mental disorders. The most common include post traumatic stress symptom, internalizing symptoms such as depression and anxiety, and externalizing behaviour.

Instead, there are few studies on infectious diseases in this population, even if unaccompanied minors are considered to be at particular risk of infectious diseases, such as hepatitis B (HBV), hepatitis C (HCV), syphilis and latent tuberculosis (LTBI), as they come from highly endemic countries for these infections. Additionally, many of them are sexually active, and remain for long periods in harsh living conditions before and during migration.

The study "Prevalence of latent tuberculosis infection, hepatitis B, hepatitis C, and syphilis among newly arrived unaccompanied minors living in reception centers in Rome" is the only Italian study and the one with the largest case history (879 minors) that aimed to estimate the prevalence of LTBI, HBV, HCV and syphilis among a population of unaccompanied immigrant minors hosted in reception centers in Rome, Italy. Similar to previous studies in adult population, the research demonstrated that immigrant minors are generally healthy and do not represent a relevant risk to public health in terms of infectious disease incidence in the native population and infectious disease outbreaks. Unfortunately, this study did not include screening for NTDs because it had begun years before the publication of the Italian guidelines in which the need for serology for schistosomiasis and strongyloidiasis was also formalized. It would have been interesting to know the prevalence of the two NTDs in this big population, also in view of the potentially severe complications they may cause.

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Prevalence of latent tuberculosis infection, hepatitis B, hepatitis C, and syphilis among newly arrived unaccompanied minors living in reception centers in Rome

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ABSTRACT

Objective: This study aimed to address the prevalence of infectious diseases in a population of unaccompanied immigrant minors living in reception centres of Rome, Italy.
Methods: The study was carried out from January 2013 to January 2019. All unaccompanied immigrant minors were screened for hepatitis B, hepatitis C, syphilis and latent tuberculosis infection.
Results: A total of 879 unaccompanied immigrant minors, 858 males and 21 females, aged 13–18 years old were studied. Of these, 615 were from Africa, 179 from Asia and 84 from Eastern Europe. A low prevalence of HBsAg carriage (2.5%) was observed as was very low prevalence of hepatitis C (0.72%) and latent syphilis (0.4%); latent tuberculosis, defined as tuberculin skin test (TST)+ X-ray case, was diagnosed in 102 (12%) minors.
Conclusions: Similar to previous studies, these data demonstrate that migrant minors are generally healthy. However, given the relatively high prevalence of hepatitis B and latent tuberculosis, systematic screening for these diseases among immigrant minors immigrants is highly recommended for early detection and treatment of potentially transmissible diseases.

Introduction

Unaccompanied immigrant minors are defined as foreigners or stateless persons aged <18 years who have immigrated without family members or other caregivers. This group includes minors who are left unaccompanied after they have entered the destination country (UNCRC Committee on the Rights of the Child, 2005). In Italy, there are approximately 1 million foreign minors, and, as of 31 October 2019, 6566 are unaccompanied children housed in dedicated reception centres spread out across the country (https://www.lavoro.gov.it/temi-e-priorita/immigrazione/focus-on/minori-stranieri/Documents/Report-MSNA-mese-ottobre-2019.pdf). As of 30 June 2019, there were 1245 reception centres. The Italian regions that have the largest number of centres are Sicily (27.4%), Lombardy (11.1%), Emilia-Romagna (8.7%), Campania (7.9%) and Lazio (7.3%) (https://www.lavoro.gov.it/documenti-e-norme/studi-e-statistiche/Documents/Report%20di%20monitoraggio%20I%20semestre%202019%20-%20I%20Minori%20Stranieri%20Non%20Accompagnati%20MSNA%20in%20Italia/Report-di-monitoraggio-MSNA-I-semestre-2019-30062019.pdf). Most of the unaccompanied minors are males (93.9%), aged 17 years (61.5%) and from Albania (25.0%), Pakistan (8.9%), Egypt (8.2%), Ivory Coast (5.8%) and Gambia (5.3%). Altogether, these five citizenships represent more than half of the unaccompanied immigrant minors in Italy (https://www.lavoro.gov.it/temi-e-priorita/immigrazione/focus-on/minori-stranieri/Documents/Report-MSNA-mese-ottobre-2019.pdf).

Unaccompanied immigrant minors are considered to be at risk of infectious diseases, such as hepatitis B (HBV), hepatitis C (HCV), syphilis and latent tuberculosis (LTBI), as they come from highly endemic countries for these infections. Additionally, most of them are sexually active, and remain for long periods in harsh living conditions before and during emigration (Baauw et al., 2019; Shetty, 2019). The screening for these infectious diseases among unaccompanied migrant minors ensures early diagnosis and treatment to

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persons hosted in the reception centres and, ultimately, may limit the circulation of infections in the whole population.

This study aimed to describe the prevalence of HBV, HCV, syphilis and LTBI in a population of unaccompanied immigrant minors living in reception centres in Rome, Italy.

Materials and methods

Study population

The study was carried out at the paediatric infectious unit of the INMP, Rome, from January 2013 to January 2019. Unaccompanied minors were recruited upon their arrival at the reception centres in Rome. All minors included in the study underwent a complete medical examination. In case of signs and symptoms suggestive of pathologies in progress and/or active pulmonary or extrapulmonary tuberculosis (TB), instrumental and microbiological diagnostic tests were carried out and sent to the Infectiology Hospital, as the current institute only provides out-patient care. All minors were screened for HBV, HCV, syphilis and LTBI, according to the prescription of the medical doctor who was in charge of the minor and, after its release, the Italian guideline *Border checks kept in check*. An unaccompanied minor's recruitment occurred in the presence of a legal representative, who gave consent for diagnostic procedures provided by the screening protocol.

Diagnostic tests

The minors were tested for hepatitis B surface antigen (HBsAg), anti-hepatitis B surface (HBs) antibodies, anti-hepatitis B core (HBc) antibodies and anti-hepatitis C virus (HCV) antibodies. Anti-HBs and anti-HBc antibodies were detected by commercial immunoassay methods following the manufacturer protocols. HBsAg was detected by electrochemiluminescence immunoassay (ECLIA) and anti-HCV antibodies by enzyme-linked immunosorbent assay (ELISA). In the presence of anti-HCV positivity, HCV infection was further confirmed by PCR. Screening for syphilis was performed by a reverse syphilis test algorithm, which starts with an assay to measure specific IgM and IgG antibodies to *Treponema pallidum* (*T. pallidum*) (TPA). Samples reactive by the TPA screen were tested by rapid plasma reagin to assess disease activity. If that test was negative, the sample was tested by a second *T. pallidum*-specific test–*T. pallidum* particle agglutination, TP-PA–to confirm the initial TPA screen. Screening for LTBI was performed with the tuberculin skin test (TST). The TST was considered positive if, at the site of the intradermal tuberculin injection, the transverse induration diameter at 72 h was at least 10 mm. Interferon-γ release assays (IGRA test) were performed in about 50% of individuals who were TST-positive because of the high costs, lack of uniform and standardised protocols followed by medical doctors who prescribed the diagnostic tests, and movement of the minors between the reception centres. All TST-positive subjects and TST/IGRA-double positive subjects were referred for chest X-rays. If the chest X-rays were negative, TST and TST/IGRA-positive migrants were considered as LTBI carriers and standard prophylactic treatment (isoniazid for 6–9 months) was offered free of charge. Vaccine records of minors were unavailable and none of those who screened for LTBI had a history of prior treatment. All minors who were positive for HBV, HCV and LTBI were referred to the infectious disease hospital to complete the diagnostic tests and receive treatment. Active immunisation was offered to minors who were susceptible to HBV infection.

Statistical methods

The statistical analysis was performed by using the Chi–square test for comparison of proportions. Logistic regression was used in order to assess the association between positive results to screening tests and sociodemographic characteristics of unaccompanied immigrant minors, controlling for mutual confounding. The STATA software 11.0 version was used.

Results

Patients

From January 2013 to January 2019, 879 unaccompanied immigrant minors hosted in centres in Rome were screened for latent TB, HBV, HCV and syphilis. The sociodemographic characteristics of minors are reported in Table 1. They came from different countries: 52% of them were from Northern Africa, 20% from Southern Asia, 18% from Sub-Saharan Africa and 10% from Eastern Europe. The mean age was 16.5 years (range 9–18), 98% were male and 571 were 17 years old.

Tuberculosis screening

Of the 879 unaccompanied minors, 834 (95%) underwent a TST. The intradermal test was positive in 102 (12%) of them. Half of the TST-positive minors (n = 48) were investigated for IFN-g release by Ag-specific T cells by IGRA and 26 (54%) had a positive result. However, the IGRA test was not performed in the remaining 54 TST-positive minors. All subjects with a positive TST and positive TST/IGRA underwent a chest X-ray, which was negative in all cases. The prevalence of LTBI was 12%, when defined by TST-positive and chest X-ray negative; if these results were applied to the entire study population, the prevalence of LTBI (double positivity TST/IGRA and negative chest X-ray) would be 6.6%. Treatment for latent TB was proposed for all subjects with a positive TST or TST/IGRA and negative chest X-ray.

Crude and adjusted odds ratios for the relationship between positive tuberculin skin test and country of origin, permanence in Italy, age and sex are shown in Table 2.

Country of origin was a strong predictor of positivity: in particular, minors coming from Sub-Saharan Africa were four times more likely to have a positive TST/IGRA result compared with those from Eastern Europe (considered as a reference group). Moreover, after the first month of permanence, the risk of positive result increased (OR = 2.21; $p = 0.06$) and for longer permanence it remained at least twice as high ($p < 0.05$) than that observed in

Table 1
Sociodemographic characteristics of the 879 unaccompanied immigrant minors.

Characteristics	N	%
Age (years)		
≤14	35	4.0
15	76	12.6
16	197	22.4
≥17	571	65.0
Sex		
Female	21	2.4
Male	858	97.6
Country of origin		
Eastern Europe	84	9.6
Northern Africa	453	51.6
Sub-Saharan Africa	162	18.5
Southern Asia	179	20.4
Permanence in Italy (months)		
<1	131	14.9
1	247	28.1
2–3	256	29.1
4+	245	27.9

Table 2
Risk factors for positive TST results among the 834 unaccompanied immigrant minors included in the screening.

Characteristics	% positive tuberculin skin test	crude OR (95% CI)	adjusted OR (95% CI)	*p*-value
Age (years)				
≤14	8.6	1	1	
15	12.2	1.48 (0.37–5.83)	2.10 (0.51–8.57)	n.s.
16	11.3	1.36 (0.38–4.82)	1.64 (0.45–5.98)	n.s.
≥17	12.8	1.57 (0.47–5.25)	2.12 (0.61–7.35)	n.s.
Sex				
Female	5.0	1	1	
Male	12.4	2.69 (0.36–20.3)	3.85 (0.49–30.27)	n.s.
Country of origin				
Eastern Europe	8.1	1	1	
Northern Africa	10.8	1.37 (0.56–3.33)	1.38 (0.56–3.38)	n.s.
Sub-Saharan Africa	25.0	3.78 (1.51–9.42)	3.99 (1.58–10.08)*	0.003
Southern Asia	6.3	0.76 (0.27–2.14)	0.70 (0.25–1.98)	n.s.
Permanence in Italy (months)				
<1	6.2	1	1	
1	11.9	2.05 (0.91–4.65)	2.21 (0.96–5.11)	0.06
2–3	14.4	2.57 (1.15–5.74)	2.54 (1.12–5.76)	0.03
4+	13.8	2.44 (1.09–5.46)	2.36 (1.04–5.37)	0.04

n.s., not statistically significant at 10% level.

minors who had been in Italy for less than 1 month. Age and sex were not significantly associated with a positive TST and TST/IGRA result ($p > 0.1$).

Hepatitis B

The HBsAg was sought in 879 minors and 22 of them (2.5%) were positive: 12 were from Sub-Saharan Africa, seven from Bangladesh and three from Egypt. Table 3 shows the distribution of hepatitis B infection by sociodemographic characteristics of minors. The association between country of origin and the risk of HBV infection was found to be statistically significant at the 5% level, revealing a higher prevalence among minors coming from Sub-Saharan Africa compared with other regions. Minors who were investigated for the presence of HBsAg, anti-HBs and anti-HBc antibodies and who did not have active infection were 615: 467 (75.9%) were susceptible to the infection, 112 (18.2%) were vaccinated and 36 (5.9%) had a past infection. There were no statistically significant differences between age groups, as well as between males and females and between groups by length of stay in Italy. A higher prevalence of vaccinated minors was found among those who came from Northern Africa (23.9%). On the other hand, there was a greater seroprevalence of past infections (15.8%) among the children from Sub-Saharan Africa (Table 4).

Table 3
Number and percentage of HBsAg-positive immigrants by age, sex, country of origin and length of stay in Italy.

Characteristics	No.	% of HBsAg-positive
Age (years)[a]		
≤14	35	2.9
15	76	0.0
16	197	2.5
≥17	571	2.8
Sex[a]		
Female	21	0.0
Male	858	2.6
Country of origin[b]		
Eastern Europe	84	0.0
Northern Africa	453	0.7
Sub-Saharan Africa	162	7.4
Southern Asia	179	3.9
Length of stay in Italy (months)[a]		
<1	131	0.8
1	247	2.4
2–3	256	2.0
4+	245	4.1

[a] Pearson Chi-squared test: not statistically significant at 5% level.
[b] Pearson Chi-squared test: $p < 0.0001$.

Hepatitis C

HCV antibodies were found in nine (1.1%) of the 836 minors who were tested: three were vaccinated for hepatitis B and three had hepatitis B in the past; six came from Egypt, one from Nigeria, one from Bangladesh and one from Guinea. PCR was positive in six (0.72%) minors coming from Egypt.

Syphilis screening

Latent syphilis was detected in three minors (two come from Bangladesh and one from Mali) of the 692 tested (0.4%).

Discussion

This study aimed to estimate the prevalence of LTBI, HBV, HCV and syphilis among a population of unaccompanied immigrant minors hosted in reception centres in Rome, Italy. The sample mainly comprised young males aged 15–17 years who had spent several years in transit countries and left Libya by boat. The majority had fled political persecution and war, and a few of them, coming mainly from West Africa, had migrated for economic reasons.

The data revealed a low prevalence of active infectious diseases among immigrant minors. In particular, the prevalence of LTBI (TST positive and chest X-ray negative) was detected in 102 (12%) minors; among these, 26 of 48 TST-positive patients were also IGRA-positive; therefore, double TST/IGRA positive and chest X-ray negative would be 6.6% of the entire population included in the study. Although limited data were available concerning the cost-effectiveness of such a sequential approach to the diagnosis of TB, it is believed that this approach could have advantages by reducing the exposure to chest X-ray in TST-positive subjects when IGRA results are negative (ECDC SCIENTIFIC ADVICE Public health

Table 4
Distribution of Hepatitis B serological markers among minors without active infection and submitted to HBsAg, anti-HBs, anti-HBc by age, sex, country of origin and length of stay in Italy.

Characteristics	Susceptible (HBsAg- anti-HBs- anti-HBc-) % = 75.9	Vaccinated (HBsAg- anti-HBs + anti-HBc-) % = 18.2	Past infection (HBsAg- anti-HBs + antiHBc+) % = 5.9
Age (years)[a]			
≤14	71.4	25.0	3.6
15	71.4	25.4	3.2
16	78.4	16.4	5.2
≥17	76.2	17.2	6.7
Sex[a]			
Female	77.8	16.7	5.6
Male	75.9	18.3	5.9
Country of origin[b]			
Eastern Europe	90.6	9.4	0.0
Northern Africa	75.0	23.9	1.2
Sub-Saharan Africa	69.3	14.9	15.8
Southern Asia	79.9	8.2	11.9
Permanence in Italy (months)[a]			
<1	78.6	17.4	4.1
1	77.2	14.8	8.0
2–3	72.3	23.7	4.0
4+	77.0	16.3	6.7

[a] Pearson Chi–squared test: not statistically significant at 5% level.
[b] Pearson Chi–squared test: $p < 0.0001$.

guidance on screening and vaccination for infectious diseases in newly arrived migrants within the EU/EEA, 2020).

This study found that the overall completion rate for LTBI screening was higher than other studies that focused on adult migrants (Carvalho et al., 2005). The high rate of LTBI screening is due to the fact that all unaccompanied minors living in reception centres follow a defined health path, which is supervised by the person responsible for the centres.

Concerning TB screening, a few points should be addressed: first, frequent TST false positives can result from Bacillus Calmette-Guerin (BCG) vaccination in minor migrants; therefore, it is suggested to that this is confirmed with a skin test by interferon-gamma release assay, which is less confused by the BCG vaccination (D'Ambrosio et al., 2017; Gualano et al., 2019). Second, the study indicates that the occurrence of positive TST/IGRA test is considerably lower in minors residing in the centres for <1 month compared with those hosted for ≥2 months. Such a finding could be due to the greater likelihood of exposure to *Mycobacterium tuberculosis* bacilli during the trip (in conditions of overcrowding, malnutrition and deprivation) or in the first moments of arriving. Additionally, the prevalence of LTBI in minors from Sub-Saharan Africans was double compared with those coming from other regions.

It could not be excluded that, in a number of cases, TST negativity could be a consequence of an anergic state. However, all the minors included in the current screening were in good health at the clinical examination and the haematological parameters were in the normal range and not suggestive of an anergic state.

No comparable studies are known that have been carried out on unaccompanied immigrant minors in Italy. The current data show that occurrence of LTBI in immigrant minors is lower than that reported by both Italian and international studies investigating the prevalence of the disease in adult refugees (Tafuri et al., 2010; Buonfrate et al., 2018; Coppola et al., 2015; McCathy et al., 2013; Usemann et al., 2019).

Concerning other infectious diseases that were investigated, a low HBsAg carriage (2.5%) and very low prevalence of HCV (0.72%) antibodies and syphilis (0.4%) were found. Based on the current results and according to other research for adult migrants, systematic screening of healthy asymptomatic unaccompanied minors who have recently arrived in Italy results in questionable for hepatitis C and syphilis, given the low observed prevalence (Buonfrate et al., 2018).

According to the Italian guidelines (https://www.inmp.it/lg/LG_Migranti-integrata.pdf) screening for HCV infection should be only offered to migrants from countries with an HCV prevalence of >3% and, regardless of their country of origin, to subjects with risk factors (HIV infection, past blood or blood product transfusions, drug addiction, abnormal liver function tests, practices that foresee perforation of the skin for non-therapeutic reasons). Also, Egypt has the highest global prevalence of hepatitis C infection, and in the current study there were 433 Egyptians, of which 419 were screened for hepatitis C; six minors were positive (1.4%). This value is lower than other studies on adult migrants, possibly due to the young age of the participants included in the study and, therefore, the limited temporal exposure to the virus.

Similarly, a blood test for syphilis is recommended for all subjects aged ≥16 years from high burden countries for HIV (HIV prevalence estimates of >1%) as well as for those who, after adequate counselling, believe that they have been exposed to risk factors. In contrast, particular attention should be paid on early detection of LTBI (Thee et al., 2019; El-Hamad et al., 2015) and hepatitis B (Gualano et al., 2019; El-Hamad et al., 2015), since early diagnosis and treatment of these infections have a huge impact on both the single migrant and community. Screening for LTBI is highly recommended, given the much higher occurrence of LTBI found in minor migrants coming from high burden countries (such as those of Sub-Saharan Africa) (https://www.inmp.it/lg/LG_Tubercolosi.pdf; Bennet and Eriksson, 2017; Greenaway et al., 2018).

A limitation of this study is related to the characteristics of the population examined. Being almost completely comprising males, possible sex-related differences in the risk distribution of the considered infections was unable to be assessed. Additionally, the population comprised a very limited number of minors aged <14 years. Therefore, prevalence of the diverse infectious diseases investigated in the present study was not stratified by age. A second limitation was the lack of data concerning HIV infection, due to the exclusion of HIV testing from health checks for age-related ethical reasons. However, Italian guidelines recommended that HIV testing only be performed in the presence of risk factors.

In this population of unaccompanied minors, no risk factors were declared or suspected by the medical doctor. Lastly, 50% of individuals with TST positivity underwent IGRA testing, as a consequence of the high costs, lack of uniform and standardised protocols followed by medical doctors who prescribed the diagnostic tests and movement of the minors between the reception centres. Similarly, the viral liver markers very often requested by the prescribers included the HBsAg and not the anti-HBC antibodies, making the overall data incomplete.

Conclusion

Similar to previous studies, the current data demonstrate that immigrant minors are generally healthy and do not represent a relevant risk to public health in terms of infectious disease incidence in the native population and infectious disease outbreaks (https://www.inmp.it/pubblicazioni/WHO-INMP_Health_Refugees_Summary.pdf).

However, as recommended by the Italian guidelines or other studies and documents (Kloning et al., 2018; Public health guidance on screening and vaccination for infectious diseases in newly arrived migrants within the EU/EEA en of disease in migrants' countries of origin), prompt and effective screening for certain infectious in migrants is recommended using a single and targeted protocol for early diagnosis. This approach may allow a real and uniform picture of the health status of immigrant minors, which is useful to fight stigma and also to implement relevant health policies.

Conflicts of interests

The authors declare no conflicts of interest.

Founding source

None.

Ethical approval

Approval was not required.

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In the study “Screening of schistosomiasis, strongyloidiasis and sexually transmitted diseases in Nigerian Female Sex Workers living in Rome”, another neglected and invisible population was considered, that of trafficked Nigerian women. Different studies have shown that sex workers may be at risk for several health issues, including those related to mental and sexual health which, in this population, are exacerbated by the experience of discrimination and stigma, leading to reduced health service access.

From the point of view of infectious diseases, several studies have investigated the prevalence of sexual infections in this group of women, however, although neglected tropical diseases such as schistosomiasis and strongyloidiasis are common in their countries of origin, no one has ever investigated the presence of these parasitic infections in this group.

Our result showed a higher seroprevalence of the two NTDs than of the STDs, so we stressed the importance of schistosomiasis and strongyloidiasis screening which have considerable clinical and public health impact.

In addition, having looked at a group of young women guests of reception centers in network with the NHS, the study showed how a prompt reception that helped overcome access barriers (cultural, financial, legal, linguistic) to the essential health care service, can reduce the risk of contracting infectious diseases in a population considered to be at high risk.

pathogens

MDPI

Article

Screening of Schistosomiasis, Strongyloidiasis and Sexually Transmitted Infections in Nigerian Female Sex Workers Living in Rome

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Abstract: Background: Female Sex Workers (FSWs) are at high risk for acquisition and transmission of sexually transmission infections (STIs). Although several studies investigated the diffusion of STIs in this population, none of them investigated the occurrence of helminth infections in FSW coming from endemic regions. This study aims to assess the prevalence of STIs and helminth infections in a cohort of FSWs. Method: authors conducted a prevalent, observational, and descriptive study on 97 Nigerian FSWs aged 17 to 52 years from January to December 2020. Results: a total of 97 FSWs were recruited. Of these, only 82 had completed screening for hepatitis B, C, syphilis, and HIV, while all 97 were screened for schistosomiasis and strongyloidiasis. The prevalence of STIs among FSWs in Rome was lower than in other European countries. The overall prevalence of HIV and HBsAg were 1.2%, (1/82) and 2.4% (2/82), respectively, while no case of hepatitis C and syphilis was found. Regarding parasitological screening, the overall prevalence of schistosoma species was 4.1% (4/97) while 5.15% (5/97) were positive for strongyloidiasis. Conclusions: our study shows a low prevalence of STIs in Nigerian FSWs except for Hepatitis B and a higher prevalence of schistosomiasis and strongyloidiasis. The permanent monitoring of STI and parasitic infections in sex workers coming from Africa is strongly warranted, especially for hepatitis B, schistosomiasis and strongyloidiasis, to allow a timely diagnosis and treatment, and to plan preventive strategies.

Keywords: FSWs; schistosomiasis; strongyloidiasis; STIs; migrants; health access barriers; helminth infections

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1. Introduction

In Italy, the number of Nigerian migrant women carrying out prostitution activities has increased in the last years, with important health implications [1,2]. According to the report of the International Organization for Migration (IOM) [3], 55% of women in prostitution in Italy are foreign-born and 36% of them come from Nigeria. IOM maintains that about 80% of Nigerian female migrants who arrived by sea in 2016 ended up being exploited as sexual slaves. The victims are very young girls, mostly minors, coming from different regions of Nigeria: Edo, Delta, Lagos, Ogun, Anambra, Imo. Different studies have shown that sex workers may undergo vulnerability for several health issues, including those related to mental and sexual health which, in this population, are exacerbated by the experience of discrimination and stigma, resulting in reduced access to health services [4]. Additionally, the high rates of alcohol abuse [5] and experiences of violence as reported in the literature [6] contribute to the vulnerability of this group of women.

From the point of view of infectious diseases, several studies have investigated the prevalence of sexual infections in this group of women. However, although neglected tropical diseases such as schistosomiasis and strongyloidiasis are common in their countries of origin, no study to the best knowledge has investigated the presence of these parasitic

infections in this group. The timely diagnosis and treatment of STIs in FSW are important in order to understand the prevalence of these infections and plan appropriate prevention and control strategies. Instead, the diagnosing and treating of strongyloidiasis and schistosomiasis offer the opportunity to avoid serious chronic complications in those with the infection and need to be considered a priority, even if they are causing no harm to the autochthonous population.

This study describes the prevalence of hepatitis B (HBV), hepatitis C (HCV), syphilis, human immunodeficiency virus (HIV) and schistosomiasis and strongyloidiasis infection in Nigerian Female Sex Workers attending the National Institute for Health, Migration and Poverty (INMP) in Rome, according to the Italian [7] and ECDC guidelines [8].

2. Materials and Methods

2.1. Ethical Aspects

The study was approved by the Ethical committee of the Italian Higher Istitute of Heatlh (Istituto Superiore di Sanità –PRE-712/16) on 30 July 2019.

2.2. Type of Study

Longitudinal, prevalence study.

2.3. Study Population

The present study was carried out in the INMP gynecological and infectious units, from January 2020 to December 2020. The study population consisted of Nigerian women who were recruited soon after (around three months) their arrival by contacting the local reception centers where they were hosted and proposing training sessions on some gynecological and infectious issues and free medical examinations. All the Nigerian women included in the study underwent a complete gynecological and medical examination. A cultural mediator was also present during the counselling activity in order to facilitate and strengthen the relationship between the FSWs and the health service. When necessary, patients were referred to gynecological or infectious disease departments for further investigation or hospitalization.

2.4. Diagnostic Tests

All women registered with the Italian National Health System were tested for hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), hepatitis B core antibody (HBcAb).

Antibodies and anti-hepatitis C virus (HCV) antibodies. All assays for HBV and HCV were detected using ELISA (Beckman Coulter, Inc, Fullerton, CA, USA). Anti-HBs and anti-HBc antibodies were detected using commercial immunoassay methods following the manufacturer protocols. HBsAg was detected via an electrochemiluminescence immunoassay (ECLIA) and anti-HCV antibodies via an enzyme-linked immunosorbent assay (ELISA). Screening for syphilis was performed via a reverse syphilis test algorithm, which starts with an assay to measure specific IgM and IgG antibodies with the *Treponema pallidum* (*T. pallidum*) (TPA). If the TPA screen was reactive, samples were tested for rapid plasma reagin to assess disease activity. If this test was negative, the sample was tested for a second *T. pallidum*-specific test—the *T. pallidum* particle agglutination, TP-PA—to confirm the initial TPA screen. Screening for HIV infection was performed using an ELISA (Beckman Coulter, Inc.), and a Western blot (Fujirebio Diagnostics) was used as confirmatory test.

Serological tests for strongyloidiasis:IFAT diagnostic procedure is an in-house method implemented at the IRCCS Sacro Cuore Don Calabria hospital. It detects IgG antibodies against *S. stercoralis* for antigen preparation, intact *S. stercoralis* filariform larvae are obtained from a positive charcoal fecal culture. A positive result is defined as a titre $\geq$ 1:80. Bordier ELISA (Bordier Affinity Products, Lausanne, Switzerland) detects Strongyloides IgG antibodies by using somatic antigens from the larvae of *Strongyloides ratti*. The test was performed as per the manufacturer's instructions. However, as the cut-off varies between

runs, we use a normalized optical density (OD) ratio to compare the results obtained in different sessions. A ratio ≥ 1 defines positive results.

Serological tests for schistosomiasis: Bordier ELISA (*Schistosoma mansoni* ELISA kit, Bordier Affinity Products SA, Crissier, Switzerland) detects Schistosoma IgG antibodies by using antigens from an adult of *S. mansoni*. The test was performed as per the manufacturer's instruction. In order to be able to compare results from different runs, we defined as positive samples those with: the optical density (OD) of the study sample/OD of weak positive serum ≥ 1 (normalized OD). Schisto II Western Blot IgG. (SCHISTO II WB IgG test LDBIO Diagnostics, Lyon, France) The test strip is able to detect *S. mansoni* + *S. haematobium* antigen strips. The test was performed as per the manufacturer's instructions using a semi-automated instrument (Dynablot, DYNEX Technologies, Buštěhrad, Czech Republic). Schistosoma ICT IgG-IgM (LDBIO Diagnostics, Lyon, France). This immune-chromatographic test (ICT) was carried out according to the manufacturer's instructions. The tests were considered as positive or negative depending on whether or not a colored band had appeared.

Urine microscopy: the urine was shaken and filtered through a 25-mm diameter small meshed filter (12 µm Nucleopore), and finally placed on a labeled slide and examined under a microscope (100×) for the detection of Schistosoma eggs.

Stool microscopy: a single stool sample per patient was fixed in 4% formalin, submitted to the formol–ether concentration and examined (100× magnification).

DNA detection using RT-PCR from faeces: a single stool sample per patient was collected in 99.8% ethanol. The DNA extraction and RT-PCR analysis was performed as previously described by Formenti et al. [9].

DNA detection using RT-PCR from urine: a single urine sample was obtained (from 10 a.m. to 12 a.m.) for each patient. DNA extraction and RT-PCR were performed as previously described. For the DNA extraction, we followed the protocol published by Pomari et al. [10].

All biological samples were collected at the INMP. Aliquots were sent to the laboratory of San Camillo hospital, Rome, for the full blood count and HIV, HBV, HCV, syphilis screening. Other samples were sent to the Department of Infectious and Tropical Diseases and Microbiology, IRCCS Sacro Cuore Don Calabria Hospital in Negrar, Verona, to perform the helminthes screening. All positive individuals at any screening test were referred to the INMP specialists on infectious diseases for the appropriate clinical management, and active immunization was offered to women who were susceptible to HBV infection.

The results were then anonymously entered in an Excel database.

3. Results

From January to December 2020, 97 FSWs, aged 17 to 52 years, were recruited. Their period of stay in Italy was less than 3 months and they had been practicing prostitution for about 3–6 months. The mean age of onset of sexual activity was 20 years. No women reported using drugs. All 97 women were screened for *Schistosoma* spp. and *S. stercoralis* whereas only 82 out of 97 (84.5%) were screened for hepatitis B, C, syphilis and HIV, due to the lack of an Italian health card. The overall seroprevalence of *Schistosoma* spp. was 4.1% (4/97), while 5.1% (5/97) were positive for strongyloidiasis. No fecal or urine tests were positive for schistosoma, whereas one fecal molecular test was positive for strongyloidiasis. In only one case was a woman positive for both helminth infections.

Results regarding schistosomiasis and strongyloidiasis screening using different tests are shown in Table 1.

Table 1. Schistosomiasis and strongyloidiasis screening methods.

PARASITE	ELISA Pos	WB IgG Pos	Urine PCR	Urine Microscopy	Stool PCR	Stool Micrcopy
Schistosoma spp. n 97	4/97 (4.1%)	4/97 (4.1%)	0/97	0/97	0/97	0/97
Strongyloides stercoralis n 97	5/97 (5.1%)	-	-	-	1/97(1%)	0/97

Regarding the STI screening, none had been previously screened either in their countries or in Italy. One woman was HIV positive and two were positive for HBsAg, while none were positive for hepatitis C or syphilis. Regarding screening for hepatitis B: eight patients (9.7%) had had a previous infection (anti-HBs and -HBc positive) and five (6%) were vaccinated, of whom all had a protective antibody titer. STI screening results are shown in Table 2.

Table 2. STI screening results.

Patients n 82	Anti-HIV	HBsAg+	Anti HCV	Syphilis Serology
	1/82 (1.2%)	2/82(2.4%)	0/82	0/82

4. Discussion

In our cohort of eighty-two screened FSWs, one (1.2%) was positive for HIV, two (2.4%) were HBsAg positive and eight (9.7%) had had previous episodes of HBV infection. Of the 82 women screened for STIs none were positive for syphilis or hepatitis C. Compared to other series published in the literature [2,11], we found a lower prevalence of STIs in our sample. A systematic review by Platt et al. [10] had found a higher prevalence of STIs with a higher prevalence of HIV infection in FSWs from Africa than FSWs from other regions, in accordance with the high prevalence of HIV/AIDS in Africa. FSW remain at risk for HIV; however, in our population the short duration of the sex work did not allow us to measure such risk. Data from an Italian study [12] on African FSWs showed a 3.5% prevalence of HBsAg, and a prevalence of HBcAb in 44%. Another study [13] showed a high prevalence of hepatitis B virus among FSWs in Nigeria compared to other groups, demonstrating that active sexual transmission is an important factor in the spread of HBV in this country where HBV is endemic, and that sex workers have a crucial role in maintaining and transmitting the virus. However, in the literature, variability in the prevalence of HBsAg and STI among Nigerian prostitutes do exist [11,14]: in particular, in another Italian study conducted by Prestileo et al. [15], none of the Nigerian prostitutes screened tested positive for HBsAg, Hepatitis C or syphilis. The lower prevalence of hepatitis B and C in our population may have several explanations: the young age of our patients; the relatively short period of prostitutionand the delay of sexual initiation compared to other studies. Moreover, the girls lived in reception centers where they received condoms and information about safe sex. In our study, the rate of hepatitis B vaccination among immigrate women is also very low (6%), so dedicated programs should be implemented. Furthermore, there was no drug addiction among the screened population. In accordance with other studies [16], sexual transmission is not a primary route of transmission for HCV infection. In addition, while hepatitis B is generally acquired in the countries of origin of immigrants from sub-Saharan Africa, where there is a high prevalence of HBV, HCV is generally less prevalent in Sub-Saharan Africa, being more prevalent in western Europe [17,18].

Studies conducted in Africa showed a low prevalence of syphilis in West Africa [19].

Moreover, the women in our study had been present in Italy for a short time and did not have their own partner. Some studies have shown that FSWs have a higher risk of contracting STIs from their non-paying sexual partners than from their clients [20,21].

Nevertheless, our screening, as well as other studies carried out on immigrants in general [22,23], show a higher seroprevalence of schistosomiasis (4.1%) and strongyloidiasis (5.1%) also in asymptomatic individuals.

In agreement with other researchers [24], we observed that seroprevalence findings were higher than stool-based figures for both parasites, supporting the use of serological screening because of their higher sensitivity, as indicated by Italian and European guidelines [7,8].

Direct methods have a specificity of 100% but their sensitivity varies with the prevalence and intensity of infection, as well as with the number of specimens collected and

slides prepared for microscopy, stool consistency and circadian and day to day variation of egg counts in stool and/or urine [25,26].

A diagnosis of schistosomiasis via the detection of specific antibodies is more sensitive than microscopy, particularly in light infections [26]. The lower likelihood of a positive direct stool examination in light intensity infections is a common occurrence in the context of screening, and also likely contributed to the poor stool detection rates in our study.

Regarding the stool and urine real-time polymerase chain reaction (PCR), some studies [27,28] have shown that the accuracy of the stool and urine PCR was similar to microscopy, indicating that this method also lacks sensitivity.

In our study, due to logistical problems of migrants who often lived far from our hospital and the cultural barriers that made them reluctant to deliver stool samples due, only one stool and urine sample was collected per patient, and this too can also explain suboptimal results.

Regarding the diagnosis ofstrongyloidiasis, the microscopy stool examination has an extremely low sensitivity for *S. stercoralis*, and even if stool PCR are more sensitive than stool microscopy, the faecal polymerase-chain reaction sensitivity is still unsatisfactory [29]. So far, serology is the method that also demonstrated the best sensitivity in the diagnosis of strongyloidiasis.

However, although antibody tests do not distinguish between past and current infection, serology is useful for identifying asymptomatic people who may have been exposed and may benefit from treatment.

Infact screening for schistosomiasis and strongyloidiasis is critical since these infections can potentially cause chronic health problems and serious consequences with high risk of potentially fatal complications [30].

Strongyloidiasis is a soil-transmitted helminth infection, with the ability to persist and replicate within a human host for many years as a result of an autoinfection cycle. Under immunosuppressant conditions (such as corticosteroid therapy, organ transplantation and human T-lymphotropic virus 1 infection) it may lead to severe clinical manifestations, such as hyperinfection syndrome and disseminated strongyloidiasis [31].

Schistosomiasis is an infection transmitted through freshwater exposure from the ova shed via the stools (*S. mansoni*) or urine (*S. haematobium*) of infected hosts. Potentially serious long-term complications result from the host immune response to the schistosome eggs: *S. mansoni* can cause fibrosis of the liver, while *S. haematobium* is associated with bladder neoplasia [32].

Unfortunately, the delayed diagnosis of strongyloidiasis and schistosomiasis, often due to a lack of clinical suspicion [33,34], nonspecific clinical presentation, and the use of inappropriate, poorly sensitive diagnostic tests, has long caused an underestimation of the actual global burden of both infections [35,36].

5. Limitation of this Study

The small number of women enrolled is a limit of this study. Due to operational reasons, the recruitment lasted only 6 months. Moreover, it is particularly difficult to reach the population [2,11]. Our study may not reflect the overall prevalence of STIs in Nigerian immigrants engaged in prostitution for the following reasons: we recruited women hosted in reception centers where they could already receive information on STIs and free condoms; all women subjected to screening recently arrived in Italy and were forced into prostitution for a short time; no one was a drug user. Last, unfortunately not all the women included in the study could perform all the STIs screening tests due to a lack of health insurance.

6. Conclusions

Our study strongly warrants a permanent monitoring of STI and parasitic infections in sex workers coming from Africa, according to the Italian and European guidelines [7,8], in order to allow a timely diagnosis and the appropriate treatment, and to plan preventive strategies in this vulnerable and marginalized population. In particular, we stress the

importance of schistosomiasis and strongyloidiasis screening, two neglected diseases often underestimated due to their asymptomatic or paucisymptomatic expression in the chronic phase, but which have considerable clinical and public health impacts [23].

At the same time, providing training sessions and guidance activities for this population is essential, considering that many patients were unable to perform the exams because they did not have the Italian health card, albeit being legally entitled to get it.

In order to implement and improve screening and counselling activities for these women and to ensure adequate access to health services, it is necessary to consider barriers to healthcare access often related to linguistic and cultural issues, as well as concerns related to their status of undocumented immigrants.

Prevention programs should take into account all social and cultural factors in order to improve their trust in public health services.

According to our experience, we believe that STI prevention and control are crucial for involving FSWs in specific educational programs with a multidisciplinary group of professionals (gynecologist, infectivologist, psychologists, transcultural mediators, lawyers, nurses, anthropologists, social workers), to improve their awareness about risk behavior, and provide all the necessary support. A cultural mediator is always present during counselling activities in our clinical settings, in order to facilitate and strengthen the relationship between the overall health system and the patient, as well as to focus on STI acquisition risk and the importance of promoting safe sex. Indeed, we have found that most women had an insufficient knowledge of the risk of STI acquisition and its prevention before they are informed in the centers about them and the practice of safer sex.

Ultimately, our study shows how thee early identification and reception of trafficked women in centers networked with health services is important for their health and access to health facilities, the prevention of infections and timely care in case of illness. Good reception breeds good health!

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Institutional Review Board Statement: This study was approved by the Ethical committee of the Italian Higher Istitute of Health (Istituto Superiore di Sanità—PRE-712/16) on 30 July 2019.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Conflicts of Interest: The authors declare that they have no conflict of interest.

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CHAPTER 3 – GUIDELINES FOR THE SCREENING OF INFECTIOUS DISEASES IN MIGRANTS

The variability in screening protocols and the lack of standardisation of health assessments on newly arrived migrants have suggested the need for evidence-based recommendations in this field to avoid the fragmentation of practices.

The following article summarizes the joint work of three public Italian institutions, the National Institute for Health, Migration and Poverty (INMP), the National Institute of Health (ISS) and the Italian Society of Migration Medicine (SIMM), aimed at producing clinical-organizational guidelines (GLs) for the health protection and the social and health care of migrant populations.

As a result, evidence-based recommendations were formulated: signs and symptoms of specific diseases should to be actively searched for active TB, malaria, STI, intestinal parasites, besides non infectious conditions such as diabetes and anaemia. In case of asymptomatic people, screening for LTBI, HIV, HBV, HCV, STI, strongyloides, schistosoma, as well as for diabetes should be offered, based on the geographical origin or on the exposure to known risk factors.

A similar document, but limited to infectious diseases, was published by ECDC in 2018. The two guidelines recommend similar measures except for tuberculosis and hepatitis C.

In both documents, screening for schistosomiasis and strongyloidiasis has been formalized for the first time.

Both schistosomiasis and strongyloidiasis have characteristics which make them appropriate for screening: most infected subjects are asymptomatic and unaware of infection or complain of very mild unspecific symptoms; both are chronic conditions; both infections can cause potentially severe conditions that could be safely prevented by an early screening and treatment; the drugs used for treatment of both are usually well tolerated and safe with few exceptions.

It was not easy to draw up guidelines on this topic because there are little data on the burden of these diseases among migrants in the EU/EEA and most publications were on small observational studies. A study conducted by Beltrame A et al. in Italy in 2017 (7) showed for schistosomiasis a prevalence higher than 17% in sub-Saharan African migrants, only considering certain cases with egg detection in faeces or urine. For strongyloidiasis, data derived from refugee populations originating from south-east Asia and Africa showed prevalence rates of between 0.8% and 4.3% using stool microscopy; higher rates of between 9% and 77% were reported using serum antibody-detection assays in refugees from south-east Asia in the EU/EEA, prevalence rates of strongyloidiasis of 3.3%, 4.2% and 5.6% were reported in Italy, Spain and France, respectively, mainly in migrant populations or expatriates,

without any reference to the diagnostic methods.

In the following paper “Health assessment for migrants and asylum seekers upon arrival and while hosted in reception centres: Italian guidelines” to which I contributed as a member of the technical group and the writing committee, we summarize the development process and the final recommendations of the Italian Guidelines (GLs).

However, it must be stressed that the guidelines have not been implemented by regional governments which are responsible for local health services administration, probably due to budget limitations and because they are not perceived as priorities.

Therefore, despite the official, national (and European) guidelines, neglected diseases unfortunately continue to be a problem in most of this country, and migrants suffering from them remain, unfortunately, neglected.

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Health assessment for migrants and asylum seekers upon arrival and while hosted in reception centres: Italian guidelines

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ABSTRACT

Background: During 2016–17, national guidelines were developed in order to provide evidence-based recommendations on health assessments for migrants and asylum seekers upon their arrival in Italy.
Methods: Scientific literature published between 2005 and 2016 was searched in different databases. A free search was also performed on international organizations' websites in order to identify additional relevant documents. A multidisciplinary panel discussed the resulting evidence and formulated recommendations.
Results: Evidence-based recommendations were formulated: signs and symptoms of specific diseases should to be actively searched for active TB, malaria, STI, intestinal parasites, diabetes, anaemia. In case of other health conditions (latent TB, HIV, HBV, HCV, STI, strongyloides, schistosoma, diabetes), testing should be offered to asymptomatic subjects coming from endemic areas or exposed to risk factors. Mass screening is recommended for anaemia and hypertension; a pregnancy test should be considered, while inclusion in cervical cancer screening and vaccination programs is recommended.

A modulated, progressive approach was developed, covering an initial evaluation during rescue operations, a full medical examination at first line reception stage and the referral to national health services during second line reception.
Conclusions: It is important to produce and periodically update guidelines on these issues and local peculiarities should be taken into account in their design and implementation. Guidelines can not only support economic sustainability, but also counteract stigmatization dynamics.

1. Introduction

Human mobility is a test case for the ability of National Health Systems to provide effective responses to emerging health needs. Such responses involve the capacity to manage complexities by means of a systemic approach, using standardised healthcare approaches and evidence-based public health practices, while avoiding fragmentation and ad hoc solutions.

Assuming this perspective, the aim of this paper is to present the development process and final recommendations of the Ital-

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ian Guidelines (GLs) "Health assessments for migrants and asylum seekers upon arrival and while hosted in reception centres" [1]. This is the first document published in 2017 within the agreement signed in 2015 between the National Institute for Health, Migration and Poverty (INMP), in collaboration with the Italian National Institute of Health (ISS) and the Italian Society of Migration Medicine (SIMM). The Programme aimed at producing clinical-organizational guidelines on health protection, care and assistance for migrant populations.

The guidelines are focussed on infectious diseases and chronic-degenerative conditions, as well as on special conditions such as pregnancy; it does not address migrants' mental health issues, as these are covered in a separate national GL [2].

1.1. Context

In 2014, a survey involving experts from EU/EEA countries and Switzerland found that screening programs on newly arrived migrants and asylum seekers, as well as their implementation, varied across countries, suggesting the need for evidence-based recommendations on this topic [3]. Another study, focussed on infectious diseases services for asylum seekers and refugees, highlighted a lack of standardisation in health assessments, data collection, transfer of health-related information and coordination among European first-entry, transit, and destination countries [4]. In recent years, this clear fragmentation of practices encouraged many public health institutions to work in this field [5–11].

This need was felt also in Italy, especially in light of two major developments. On one side, the peak of migrants and asylum seekers' arrivals recorded in 2011 during the so-called Ärab Spring(almost 65,000) that further increased to approximately 170,000 people in 2014 and to 181,000 in 2016. As a consequence, the reception system passed from 3000 places in the first decade of this century to over 22,000 places in 2013, and then to almost 205,000 persons received in July 2017 [12].

On the other side, Legislative Decree n. 142 of 2015 [13] was introduced: this was meant to institutionally manage the flow of asylum seekers (still numerically marginal if compared to the overall stock of migrants living in Italy) through a renewed reception system, which assumed the impossibility to consider Italy simply as a transit country under EU Dublin III Regulation [14]. In this context, it was crucial to define evidence-based health protocols tailored to the various reception phases, in order to offer effective health protection to migrants and asylum seekers and to avoid the rise of speculations and prejudices.

1.2. Healthcare: from rescue to reception

These GLs intended to operate in a context where healthcare is provided at every stage of the Italian reception pathway for migrants and asylum seekers: from rescue at sea, to placement, up to integration. In particular, during rescue operations at sea, a very initial medical evaluation is provided by the Coast Guard on board the ship, and a certificate of "free circulation" is released by the "Port, Airport and Border Health Offices" (USMAF - Ministry of Health). Health assistance is then offered at the dock or at the hotspots through a collaboration of USMAF with the Local Health Unit.

First-line reception is organized in governmental Centres/Hubs, at regional or interregional level. During this phase, lasting in principle from 1 week to 1 month after arrival, asylum seekers may apply for international protection; healthcare is provided by the reception centres themselves, sometimes in collaboration with the Local Health Unit, but without direct access to the National Health System (NHS).

Second-line reception is guaranteed through SIPROIMI, the reception system dedicated to beneficiaries of international protection and to unaccompanied children, while asylum seekers can only have access to Emergency Accommodation Centres (CAS Centri d'accoglienza straordinaria). While a new legislative decree is presently reviewing SIPROIMI which will be called SAI (Reception and Integration System), redefining the target population and the type of intervention, it remains that both beneficiaries of international protection and asylum seekers have the right to mandatory registration with the Italian NHS once they apply for international protection: from this moment they are entitled to have a General Practitioner or paediatrician and can receive health care within the Essential Levels of Care, on equal terms with Italian citizens.

1.3. Purpose of the guideline and recipients

While access to healthcare is therefore always guaranteed, the GL "Health assessments for migrants and asylum seekers upon arrival and while hosted in reception centres" responded to the need to standardize protocols for healthcare of migrants and asylum seekers with pathologies which may jeopardize their own and/or public health, but also to ensure prevention and health promotion within these fragile populations. Key objectives were:

- To promote clinical and organizational appropriateness, in the frame of valid and effective pathways;
- To prevent waste connected to unnecessary or unnecessarily-repeated health assessments;
- To prevent or contain defensive practices due to possibly unjustified scaremongering.

Target readers of the GLs are, primarily: decision makers; health managers; health professionals; researchers. In addition: migrant communities; politicians; social and legal workers; NGOs personnel; media workers.

2. Materials and methods

GLs production was initiated on the base of a priority setting activity. This was based on a consultation involving INMP National Network representatives, SIMM Board and Scientific Committee members and the Immigration and Health Groups spokespersons (55 persons totally). Each participant was asked to identify and rank 5 priority topics out of a list of 16, which was previously compiled based on a literature search [15]. At the end of the consultation, "health assessments for migrants and asylum seekers upon arrival and while hosted in reception centres" scored first among the submitted topics.

The Scientific Committee coordinating the development of the GLs was formed by representatives of the three institutions promoting GLs production and was supported by a technical group. The first tasks of the Scientific Committee were to form a multidisciplinary, multi-professional panel, and to identify relevant review question topics, based on a preliminary literature search. The panel was composed of independent experts and of representatives of scientific societies, national and international institutions and health organizations particularly involved in migrants' health protection. Each scientific society, institution and organization was asked to identify one person as his or her representative in the GLs panel. Independent experts were selected among those of proven excellence in the topics covered by the GLs. The following professional profiles were involved: infectious disease, gastroenterology/hepatology, dermatology, paediatrics/neonatology and hygiene/epidemiology specialists; guideline development methodologists; one member of migrants' associations, representing the

target population; one representative of cultural mediators in healthcare settings. Each member of the panel declared no conflict of interest. During 2016–17 the panel met twice: in the first meeting members were asked to frame the review questions, based on a number of topics proposed by the Scientific Committee, who then synthesised what emerged from the discussion for the follow of the process. During the second and last meeting, panel members discussed the synthesis of included documents and formulated recommendations.

Conditions, and related questions, covered by the GL included infectious diseases (tuberculosis, malaria, HIV, HBV, HCV, sexually transmissible infections, intestinal parasites), chronic-degenerative diseases (diabetes, anaemia, hypertension, cervical cancer), pregnancy and vaccinations. A particular attention was paid to general medical examinations upon arrival and throughout the reception pathway (Table 1).

The PICO process (Population, Intervention, Comparison, Outcome) was used to formulate the search questions. Migrants and asylum seekers intercepted by the Italian reception system in any situation (catchment population) were considered as the target population; comparison between strategies (screening *vs.* active seeking of signs and symptoms) was considered as the intervention/control; early identification of disease, infection or of a particular condition (pregnancy) was the outcome of interest.

2.1. Search strategy

ISS Documentation Centre developed the search strategy for each review question and consulted the bibliographic databases. Scientific literature was searched systematically in the following databases: Medline, Embase, Scisearch, Biosis and Pascal. After a preliminary pilot search aiming at balancing recall (sensitivity) and precision (specificity), a tailored search strategy was developed and performed for each question. The search strategies included both Medline and Embase subject headings (i.e. Mesh and Emtree terms, respectively) as well as free-text words related to the subject of the 15 GLs questions (Table 1). Duplicate citations due to databases overlap were removed during each query session and de-duplicated search results were exported to Microsoft Excel to facilitate further data analysis and management.

In order to identify potentially relevant documents not indexed in bibliographic databases, an additional free search was performed on the websites of international agencies and organizations active on GLs production, on Public Health and on migration related issues.

Strategies applied to search scientific literature databases are available for consultation in Supplementary material S1.

2.2. Eligibility criteria for studies inclusion

The literature search was restricted to English and Italian documents published from 2005 to 2016. Only secondary literature was selected, in particular Systematic Reviews with or without meta-analysis and GLs, as these documents are ranked at the top of the hierarchy of evidence. Consensus Conference and Position papers were included only if based on a systematic search of the literature.

Publications needed to be related to the target population of newly arrived migrants, and to the condition covered by each question.

Documents were included only if they met the above-mentioned eligibility criteria, and after a quality assessment.

2.3. Selection and quality assessment of studies

Quality assessment was carried out using the PRISMA checklist [16] for systematic reviews and the AGREE II [17,18] instrument for GLs. PRISMA checklist was originally designed for reporting, but it may also be used for quality assessment.

The Scientific Committee identified nine Literature Reviewers: five doctors in speciality training in Hygiene and Preventive Medicine, one student with a degree in Medicine and Surgery and three researchers. A team of epidemiology and GLs development experts properly trained the Literature Reviewers. The training included a course on B̈asic methods in epidemiologyänd three meetings dedicated to the stages of guidelines development and to internationally used methodological tools; the latter had a focus on PRISMA and AGREE checklists, used for quality assessment.

Each paper was assigned to two reviewers, working independently: they assessed title and abstract, and then the full text, against the eligibility criteria. Later on, they independently assessed the methodological quality of each included study. Any disagreement between the two reviewers was solved through a discussion between them. If this was not possible, a senior researcher stepped in to solve the disagreement.

Consensus conferences were not evaluated through a checklist, but in terms of overall quality, with particular attention to the methodology used for the systematic review of literature.

2.4. Data extraction and synthesis

Relevant information from the included studies was extracted by one reviewer and checked by another. ISS experts provided two different extraction forms, one for systematic reviews and one for GLs. The first form included the following data: bibliographic reference, PRISMA quality assessment, study objectives, literature selection and evaluation, characteristics of the population, interventions, comparators, outcomes, results, conclusions, limitations identified by the authors and any comments from the reviewer. Information extracted from GL included bibliographic reference, research institution, AGREE assessment, search strategy, GL development methodology, target population, whom the GL is intended for, recommendations for each GL question and other possibly relevant data for each question.

A Writing Committee was formed by members of the Scientific Committee, of the Technical Group and of the three promoting institutions. Using the data extraction forms filled in by the reviewers, it produced the narrative synthesis of the included studies, for each GLs question.

2.5. Web platform

In order to share all documents used and produced throughout the GLs development process, a dedicated platform was created on the INMP website. Panel members and all those involved in GL production had access to it at any time. This also ensured the transparency of the process. The space was organized in sections, one for each question, containing the output of the literature search, study selection, quality assessment, data extraction and narrative synthesis. GLs drafts were located in a separate folder.

2.6. Formulation and grading of the recommendations

Based on the synthesis of the literature, the writing committee produced a first draft of the recommendations.

Evidence for each review question was presented during the final meeting of the panel. Recommendations proposed by the writing committee were discussed, until an agreement was reached. A formal vote was foreseen in the event of a disagreement; this procedure, however, was not used, as a clear agreement among panel members emerged during the discussion. After the panel meeting, the writing committee summarized what emerged from the dis-

Table 1
Guideline questions.

Q1 –	Which triage tools (e.g. SIEVE, START, SORT, CESIRA, MIMMS, SATS, etc.) are indicated to identify health conditions requiring urgent attention in migrants and asylum seekers upon their arrival?
Q2 –	Is a general medical examination of all migrants and asylum seekers indicated at the beginning of the reception pathway? Does any tool (protocols and checklists) exist to assess migrants and asylum seekers' health - including physical trauma outcomes - during a general medical examination?
Q3 –	Which is the indicated strategy for early identification of tuberculosis and of latent tuberculosis infection in migrants and asylum seekers during the reception pathway?
Q4 –	Which is the indicated strategy for early identification of malaria in migrants and asylum seekers during the reception pathway?
Q5 –	Is an HIV screening programme indicated for migrants and asylum seekers during the reception pathway?
Q6 –	Is an HBV screening programme indicated for migrants and asylum seekers during the reception pathway?
Q7 –	Is an HCV screening programme indicated for migrants and asylum seekers during the reception pathway?
Q8 –	Which is the indicated strategy for early identification of STIs in migrants and asylum seekers during the reception pathway? Is a syphilis screening programme indicated?
Q9 –	Is a parasitological stool test indicated as screening for intestinal parasites in migrants and asylum seekers during the reception pathway? Is a Strongyloides screening programme indicated? Is a Schistosoma screening programme indicated?
Q10 –	Is a diabetes screening programme indicated for migrants and asylum seekers during the reception pathway?
Q11 –	Is an anaemia screening programme indicated for migrants and asylum seekers during the reception pathway?
Q12 –	Is arterial hypertension screening via blood pressure measurement indicated for migrants and asylum seekers during the reception pathway?
Q13 –	Should a pregnancy test be offered to all migrant and asylum seeking women of reproductive age upon their arrival in Italy?
Q14 –	Is offering early cervical cancer screening indicated for migrant and asylum seeking women during the reception pathway?
Q15 –	Is an active offer of mandatory and recommended vaccinations indicated for migrants and asylum seekers during the reception pathway?

Table 2
Recommendations grading system.

Grade of recommendation	Definition
a	At least 1 high quality document (SR quality = high and/or GL score = 6–7)
b	At least 1 document of satisfactory quality (SR quality = satisfactory and/or GL score = 4–5); or at least 3 consistent low quality documents (SR quality = low and/or GL score = 1–3
c	At least 1 or 2 low quality documents (SR quality = low and/or GL score = 1–3
panel	No evidence in literature, but panel considered appropriate to add details, or to adapt the recommendation to the Italian context.

SR: Systematic Reviews.

cussion, and sent the emended document for final approval to the panel.

Based on the quality (from PRISMA or AGREE) and consistency of the studies supporting each recommendation, a 3-level rating system for grading the strength of recommendations was developed (Table 2). An additional level of grading, defined as ̈panel recommendation, was introduced: this was applied when, even in absence of specific evidence from the literature, the panel considered appropriate to add details, or to adapt the recommendation to the Italian context.

The included consensus conferences, all of high quality, did not participate in the assignment of the grade, but were consistent with the recommendations and were used to further support them.

2.7. Review and public consultation

The GLs draft remained publicly available online for three weeks, in order to receive comments and suggestions from experts and the public. The review process was supported by the INMP website (https://www.inmp.it/ita/Rete-Nazionale/Linee-Guida-Salute-Migranti) and was advertised on the websites of the other two involved institutions. The resulting comments were considered by the panel, and a part of them was accepted and included in the final text. The GLs were also submitted to four Referees: one pneumologist, one epidemiologist, one public health specialist and one moral philosopher. They were asked to assess the readability and clarity of the text and the feasibility of recommendations. Again, as for experts and the public, some comments from the referees were accepted and included in the final text.

3. Results

The systematic literature search produced 1059 documents meeting the eligibility criteria; based on titles and abstracts, 155 documents were selected for perusal of the full text. This led to a further selection of 48 documents, out of which 39 were used as a base for recommendations (the other nine being included as eligible, but not useful in terms of content).

For each question, Table 3 presents the full recommendations (and their grading) resulting from the summary of literature described below; the reference to supporting documents are indicated at the end of each of them in curly brackets.

3.1. Triage tools

With regard to triage tools related to newly arrived migrants or asylum seekers, no GL or systematic review was found.

3.2. Medical examination

With regard to medical examination, based on the systematic literature review three GLs were included [6,19,20].

All documents highlight the importance of an early medical examination for an accurate collection of the patient's medical history (with particular reference to previous health conditions, medications taken, any allergies, vaccinations and risk factors such as alcohol, smoking and drugs) and family and social history (also in relation to migration path). As the detection of signs and symptoms is concerned, the three GLs recommend the search for possible presence of cough, fever, weight loss, night sweats, respiratory and abdominal disorders, splenomegaly, diarrhoea, itching, skin lesions or rash; they recommend also an evaluation of visual acuity and of the oral cavity, of nutritional status and symptoms of anaemia, cervical, axillary and inguinal lymphadenopathies and a cardiorespiratory examination. The importance of cultural mediators is emphasized, in consideration of the difficulties experienced by many migrants and asylum seekers in their relationship with health workers. See Table 3 for recommendations.

Table 3
List of recommendations for each review question (the reference to supporting documents and Grading are indicated at the end of each recommendation in curly brackets).

Triage tools (Question 1)
Regarding triage tools, no document was found.
Medical examination (Question 2)
R2.1 – During medical examination, particular attention should be paid to medical, family and social history. Further, signs and/or symptoms suggestive of specific diseases – tuberculosis, malaria, STIs, parasitosis, anaemia and diabetes – should be detected early, in order to provide timely access to care {[6,19,20] (Grade A)}.
R2.2 – Medical examination should include a nutritional assessment, a cardio-respiratory exam, visual and auditory acuity tests, a careful skin inspection to detect possible ectoparasitosis (frequently found in recently arrived migrants and asylum seekers) and a search for any signs of trauma and/or torture {[6,19,20] (Grade A)}.
R2.3 – In consideration of the setting, all health workers should have a comprehensive understanding of the epidemiological context in countries of origin and transit. In addition, health workers should be trained in a culturally competent approach, and should receive adequate psychological support in order to manage emotionally stressful situations and avoid burnout {[6,19,20] (Grade A)}.
R2.4 – The presence of cultural mediators in healthcare settings is recommended, in order to support the doctor-patient relationship {[6,19,20] (Grade A)}.
R2.5 – The use of ICT tools to record and make medical files available throughout the reception process, while safeguarding patients' data protection rights, is recommended (Panel's recommendation).

Tuberculosis (Question 3)
Active Tuberculosis
R3.1 – Active case finding for TB disease should begin immediately, during the first medical evaluation at the dock (or at any point of entry), and should continue throughout the reception pathway {[21,26–28] (Grade A)}.
R3.2 – In order to allow timely access to diagnosis and treatment, migrants and asylum seekers should receive adequate information on tuberculosis signs and symptoms and on its modes of transmission right from first line reception stage; due attention should be paid to the patient's language proficiency and to the adaptation of message contents and the formats to the appropriate cultural system {[23,25,27–29] (Grade A)}.
R3.3 – For patients with a cough persisting for more than 2 weeks, a chest x-ray is recommended, along with further diagnostic tests {[22,27,29]}. When an x-ray cannot be performed promptly (for example, during rescue operations), a rapid TB molecular test should be performed in order to identify cases and to implement appropriate isolation measures {[26,27] (Grade B)}.
R3.4 – The use of TST or IGRA tests to identify active cases of TB disease is not recommended {[26] (Grade B)}.
R3.5 – Routine radiographic and/or microbiologic screening in asymptomatic individuals is not recommended {[22,25,27] (Grade B)}.
R3.6 – All persons with a confirmed diagnosis of tuberculosis should be guaranteed immediate and free access to treatment, continuity of care and follow up, with particular attention to those transferred to other reception centres (or to other countries) {[24] (Grade A)}.
Latent Tuberculosis Infection
R3.7 – TST or IGRA test (the latter being indicated particularly in cases of previous vaccination) should be offered to all asymptomatic subjects coming from high burden countries (TB incidence estimate >100/100.000) who are likely to be hosted in reception centres for at least 6 months {[5,6,21,26,29,37,38] (Grade A)}.
R3.8 – TST test is recommended for children aged <5 years {[19,39] (Grade A)}.
R3.9 – Subjects with positive TST (diameter ≥10 mm) or IGRA test should undergo a chest x-ray (as well as further diagnostic tests, if necessary) in order to rule out TB disease. A diameter of ≥5 mm is considered as clinically relevant in cases of serious malnutrition and of HIV seropositivity {[19,29,39] (Grade A)}.
R3.10 – Therapy for latent tuberculosis infection should be offered to all persons with a positive TST or IGRA test and a negative x-ray, in order to prevent new cases {[19,26] (Grade A)}.

Malaria (Question 4)
R4.1 – Signs and/or symptoms suggestive of malaria (particularly fever) should be detected early - right from the rescue phase and throughout the reception pathway - in migrants and asylum seekers who reportedly lived in or travelled through areas with a high malaria burden {[5,6,19,40] (Grade A)}.
R4.2 – Health workers involved in evaluating migrants during rescue operations and throughout the reception pathway should be trained in recognizing malaria and severe malaria signs and symptoms, so to avoid diagnostic and therapeutic delays {[5,6] (Grade A)}.
R4.3 – Hemoscopy should be promptly offered as initial diagnostic procedure to subjects with malaria signs and/or symptoms. Rapid tests are a valid alternative for symptomatic patients, as these are easy to use and can be resorted to even during rescue operations and first line reception {[5,19,40] (Grade A)}.
R4.4 – A diagnosis of malaria in presence of splenomegaly and/or thrombocytopenia should be considered during investigations on individuals who report having lived or travelled through countries with a high malaria burden; these two conditions, in fact, are predictors of the disease even in the absence of symptoms {[40] (Grade B)}.
R4.5 – Patients with a confirmed diagnosis of malaria should be referred to a specialist. Cases of Plasmodium falciparum malaria or severe non-falciparum malaria should be guaranteed an immediate access to care: their clinical conditions, in fact, may rapidly deteriorate, especially in the case of children, pregnant women and immunosuppressed subjects {[19] (Grade A)}.

HIV (Question 5)
R5.1 – During second line reception, all migrants and asylum seekers should be offered clear and complete counselling on HIV infection, on AIDS and on the possibility of receiving effective treatment. This information should be provided using a culturally sensitive approach, possibly in the individual's mother tongue, and through the collaboration of a cultural mediator {[5,19,42] (Grade A)}.
R5.2 – An HIV test should be offered to all subjects aged ≥16 years and coming from countries with a high HIV burden (HIV prevalence estimates >1 %); to pregnant and breastfeeding women; to those who, during counselling, report having been exposed to risk factors (past blood or blood product transfusions, drug addiction, multiple sexual partners or history of sexual abuse/violence); and to those with STI or tuberculosis co-infections {[5,6,19,43–45] (Grade A)}.
R5.3 – An HIV test should also be offered to children aged <16 years in presence of individual risk factors (seropositive mothers, early sexual activity, history of sexual abuse/violence) and/or having STI or tuberculosis co-infection {[6,19] (Grade A)}.

Hepatitis B (Question 6)
R6.1 – During second line reception, screening for HBV infection should be offered to all migrants and asylum seekers coming from countries with an HBsAg prevalence of >2 % and, regardless of their country of origin, to subjects having risk factors (HIV infection, past blood or blood product transfusions, drug addiction, multiple sexual partners, sexual abuse, close family members with HBV infection and undergoing immunosuppressive therapy), as well as to pregnant women {[5,6,47–49,51,52] (Grade A)}.
R6.2 – Screening should include HBsAg, HBcAb and HBsAb testing {[5,19,49,53] (Grade A)}.
R6.3 – HBsAg positive individuals should be referred to a specialist for further diagnostic evaluation and treatment, if needed {[19,50] (Grade A)}.

Hepatitis C (Question 7)
R7.1 – During second line reception, screening for HCV infection should be offered to all migrants and asylum seekers coming from countries with an HCV prevalence of >3 %; and, regardless of their country of origin, to subjects at risk (with HIV infection, past blood or blood product transfusions, drug addiction, abnormal liver function tests, practices foreseeing skin perforation for non-therapeutic reasons) {[5,6,19,49,52] (Grade A)}.
R7.2 – Screening should include anti-HCV testing {[5,6,19] (Grade A)}.
R7.3 – Anti-HCV positive subjects should undergo further viral load evaluation (quantitative HCV-RNA); in case of positive result, they should be referred to a specialist for further diagnostic evaluation and treatment, if needed {[5,6,19,50] (Grade A)}.

Table 3 (*Continued*)

Sexually transmitted infections (Question 8)

R8.1 – During medical examinations at reception centres, STI signs and symptoms (vaginal, cervical or urethral discharge, genital or oral warts, rash, inguinal lymphadenopathy) should be carefully searched for in recently arrived migrants and asylum seekers. Symptomatic subjects should undergo a specialist evaluation {[6,19,54] (Grade A)}.

R8.2 – During the examination, the doctor should provide adequate counselling on sexual health and on STI prevention measures {[19,54] (Grade A)}.

R8.3 – During second line reception, asymptomatic subjects with risk factors (multiple partners, new partners, recent STI, sexual violence) should be offered diagnostic tests for Chlamydia trachomatis and Neisseria gonorrhoeae, based on a first pass urine PCR, or preferably on a vaginal swab in the case of women {[6,19,54] (Grade A)}

R8.4 – During second line reception, a blood test for syphilis is recommended for all subjects aged ≥16 years and coming from high HIV burden countries (HIV prevalence estimates of >1 %); and for those who, after adequate counselling, believe they have been exposed to risk factors {[6,19,54] (Grade A)}.

R8.5 – For children aged <16 years, a syphilis test should be offered in presence of individual risk factors (seropositive mother, early sexual activity, sexual abuse/violence) or of other STIs {[19,54] (Grade A)}.

Intestinal parasites (Question 9)

R9.1 – During medical examinations and throughout the reception pathway, the presence of symptoms such as diarrhoea, abdominal pain, nausea, vomiting, itching and haematuria (including a history of the same) should be considered as being suggestive of intestinal parasites {[19) (Grade A)}.

R9.2 – During clinical investigations, the detection of eosinophilia should be considered as a possible indirect marker of helminths {[19,55,56]} (Grade A).

R9.3 – In presence of signs or symptoms compatible with intestinal parasites and/or with eosinophilia, stool microscopy should be offered to detect any intestinal parasite {[6,19,56] (Grade A)}.

R9.4 – During second line reception, a blood test is recommended for migrants and asylum seekers having lived or travelled in countries endemic for strongyloidiasis and schistosomiasis, even if asymptomatic. Subjects not recently treated and positive for Strongyloides stercoralis and Schistosoma spp should be considered as having an active infection and must be treated {[19,55,56] (Grade A)}.

Diabetes (Question 10)

R10.1 – At first line reception, level diabetes should be investigated for, by collecting a careful medical history and by searching for signs/symptoms of the disease. In symptomatic patients, a fasting blood glucose test is recommended {[7,19] (Grade A)}.

R10.2 – During second reception, glycaemic screening is recommended in asymptomatic subjects aged ≥35 years, coming from countries with a high prevalence of diabetes (the Indian subcontinent, the Middle East, North Africa and Sub-Saharan Africa) and with specific risk factors (hypertension, hyperlipidemia, family history of diabetes), in order to ensure timely diagnosis and treatment take up {[5,19] (Grade A)}.

R10.3 – All migrants and asylum seekers should receive information on disease prevention, possible complications and healthy diet and lifestyles, in an individualized and culturally sensitive manner {[57] (Grade A)}.

Anaemia (Question 11)

R11.1 – It is recommended that signs and/or symptoms of anaemia are considered right from the initial medical examination, in order to allow prompt access to treatment {[7,19,58] (Grade A)}.

R11.2 – Complete blood count should be offered to all migrants and asylum seekers as part of their health assessment {[7,19,58] (Grade A)}.

Hypertension (Question 12)

R12.1 During medical examination in reception centres, all migrants should be checked for hypertension by measuring their arterial blood pressure {[19] (Grade A)}.

Pregnancy (Question 13)

R13.1 – Pregnancy should be immediately ascertained in migrant and asylum seeking women, in order to activate the dedicated reception pathway. Right from the initial medical examination, a pregnancy test should be offered to women in reproductive age, in consideration of the risk of having been victim of sexual violence during their journey {[19] (Grade A)}.

R13.2 – In the event of a pregnancy, migrant and asylum seeking women must be guaranteed the same services foreseen by the Italian National Health Service for all women in that condition, taking into account their preference in terms of their health providers and cultural mediators' gender {[19] (Grade A)}.

[5pt] *Cervical cancer (Question 14)*

R14.1 – Early diagnosis of cervical cancer must be guaranteed to migrant and asylum seeking women aged 25–64 years, by means of their enrolment in local public screening programs {[7,19] (Grade A)}.

R14.2 – It is recommended that the interventional setting is respectful of cultural values, experiences and individual preferences, including, whenever possible, women's preference in terms of their health providers and cultural mediators' gender {[5,7] (Grade A)}.

Vaccinations (Question 15)

R15.1 – During second line reception, unvaccinated children (0–14 years) or those with uncertain vaccination records should be offered vaccinations according to the national schedule, as per their age {[5–7,19,59] (Grade A)}.

R15.2 – Adults having no or uncertain vaccination history should be offered the following vaccinations: polio, measles, mumps, rubella, chickenpox (except for pregnant women), diphtheria, tetanus, pertussis, HBV (for all screened adults testing negative on blood markers) {[5–7,19,52,59–61] (Grade A)}.

3.3. Tuberculosis

3.3.1. Active tuberculosis

With regard to tuberculosis disease, five systematic reviews [21–25], four GLs [6,26–28] and two consensus conferences [29,30] were provided by the literature review.

Many of the included documents [23,25,27–29] stress the need to offer migrants and asylum seekers adequate information on the aetiology, symptoms and mode of transmission of the disease, together with the administration of diagnostic tests and/or treatment. During medical examination, the search for signs and symptoms on all migrants and asylum seekers is recommended by four GLs: Public Health Agency of Canada [26], WHO [27], CDC [28] and Italian consensus conference [29]; HPSC GL [6] and Zenner et al. [22] recommend to restrict screening to high-risk populations (prevalence ≥40/100.000). For those patients with a persistent cough lasting longer than 2 weeks, a chest x-ray is recommended, along with further diagnostic tests [26,27,29]; whereas x-ray [22,25,27] and TST/IGRA [26] are not recommended as first line screening test. According to the Arshad et al.'s systematic review [24], in order to be fully effective, screening should be part of an integrated case management within the framework of a directly observed treatment (DOT) programme. See Table 3 for recommendations.

3.3.2. Latent tuberculosis infection

Literature search for Latent Tuberculosis Infection (LTI) produced seven systematic reviews [21,31–36], seven guidelines [5,6,19,26,37–39] and one consensus conference [29].

Four GLs [6,26,37,38], the Italian Consensus Conference [29] and Sanneh and Al-Shareef's systematic review [21] recommend screening all migrants and asylum seekers from highly endemic countries (NICE [37]: >150 cases per 100,000; WHO [38] and CC:

>100 cases per 100,000; HPSC [6] and Sanneh and Al-Shareef [21]: >40 cases per 100,000; PHA [26]: >30 per 100,000).

Australian GL [19] recommends offering LTI test to all migrants and asylum seekers aged ≤35 years, preferably within one month of their arrival in Australia. CDC GL [39] recommends screening all new arrivals for which a similar test cannot be documented at departure.

Most included documents suggest IGRA and TST to assess the presence of LTI. NICE [37], PHA [26] and CDC [39] GLs suggest using one or the other indistinctly. According to the WHO GL [38], both TST and IGRA can be used in high and middle-income countries, while TST in recommended in low- and middle-income countries. Campbell et al. [32] and Nienhaus et al. [35]'s systematic reviews consider IGRA as best choice, and preferable in cases of past vaccination (Australasian Society for Infectious Diseases ASID [19]). On the contrary, Sanneh and Al-Shareef's systematic review [21], NICE GL [37], Italian Consensus Conference [26] and, only for children <5 years old, Australian [19] and CDC [39] GLs suggest the use of TST.

According to Australian [19] and CDC [39] GLs and to Italian Consensus Conference [29], patients positive to TST or INGRA should be referred to specialist TB services and undergo chest x-ray and any other diagnostic test to exclude active TB. In these documents TST is considered as positive with an induration of ≥10 mm, or ≥5 mm in conjunction with severe malnutrition, HIV infection or immunosuppression.

The importance of treating positive migrants and asylum seekers is underlined in 2 GLs (ASID [19] PHA [26]) and in the Italian Consensus Conference [29], where LTI treatment is suggested for migrants ≤35 years or for HIV co-infected. See Table 3 for recommendations.

3.4. Malaria

With regard to malaria, a total of five guidelines [5,6,19,40,41] were included.

All documents recommend the search of malaria signs or symptoms in all migrants and asylum seekers travelling from, or having transited through, an endemic area; and the screening of symptomatic subjects. ASID GL [19] recommends screening also for asymptomatic individuals coming from endemic regions whereas, according to CDC GL [40] and Stauffer et al. [41], migrants and asylum seekers from sub-Saharan Africa should receive presumptive treatment or screening during medical examination within 3 months from arrival. CDC GL stresses the importance of considering the diagnosis of malaria in presence of splenomegaly and/or thrombocytopenia, as these are predictors of the disease even in the absence of symptoms.

Regarding the test of choice, GLs from ASID [19], CDC [40] and Canada [5] recommend blood smear microscopy and/or rapid diagnostic tests (RDT). See Table 3 for recommendations.

3.5. HIV

The literature review on HIV infection provided one systematic review [42] and six GLs [5,6,19,43–45].

All the selected GLs recommend an HIV test to be offered to all newly arrived adolescents and adults coming from high prevalence countries or exposed to risk factors; and to all pregnant women. ASID [19] and HPSC [6] GLs recommend an HIV test also for unaccompanied children exposed to specific risk factors or with co-infections, such as other sexually transmitted infections or tuberculosis.

ASID [19] and the Canadian Medical Association [5] GLs and Alvarez-del Arco et al.'s systematic review [42] stress the need of an adequate counselling, in order to provide clear and complete information on HIV infection, on AIDS and on the possibility of receiving effective treatment. See Table 3 for recommendations.

3.6. HBV

Regarding hepatitis B, two systematic reviews [46,47], seven GLs [5,6,19,48–51] and two consensus conferences [52,53] were included.

HPSC [6], CDC [49,51], MoH of Singapore [48] and the Canadian Medical Association [5] GLs, the Italian consensus conference [52] and Rossi et al.'s systematic review [47] all agree on recommending HBV screening for all migrants and asylum seekers coming from high or medium endemic countries (HBsAg prevalence ≥2 %), for those with specific risk factors and for all pregnant women. GLs by ACID [19] and NICE [50] recommend the identification of dedicated therapeutic pathways in case of positivity. See Table 3 for recommendations.

3.7. HCV

The summary of evidence related to hepatitis C screenings for newly arrived migrants and asylum seekers included one systematic review [46], five GLs [5,6,19,49,50] and one consensus conference [52].

ASID [19], HPSC [6], and the Canadian Medical Association [5] GLs and the Italian consensus conference [52] recommend HCV screening for all newly arrived migrants and asylum seekers coming from endemic countries (chronic HCV prevalence ≥3 %) or exposed to risk factors. American CDC GL [49] recommends routine screening for refugees born between 1945 and 1965, for those exposed to identified risk factors or co-infections, as in the case of U.S. general population.

On the contrary, no screening limitation is foreseen by NICE [50], which recommends testing all newly arrived migrants and asylum seekers.

The only included systematic review [46] concludes that there is no evidence of cost-effectiveness for HCV screening among migrants and asylum seekers. See Table 3 for recommendations.

3.8. Sexually transmitted infections (STDs)

Three GLs were included with regard to sexually transmitted infections [6,19,54].

CDC [54] recommends to evaluate newly arrived migrants and asylum seekers for all STDs: a thorough medical history, physical examination and search for symptoms, signs or lesions consistent with these diseases is suggested. For specific asymptomatic infections, laboratory testing is recommended. For chlamydia and gonorrhoea, nucleic acid amplification tests are recommended for female migrants and asylum seekers having risk factors. For syphilis, nontreponemal testing should be offered routinely to all persons aged 15 or more and to children if at risk.

The Australian GL [19] recommends health examination for STIs in adults with particular risk factors, and/or with symptoms consistent with a STI. As for children, the GL suggests syphilis serology in unaccompanied and separated children and screening for other STIs, including HIV and syphilis, if there are clinical concerns of sexual abuse.

According to the Irish GL [6], all sexually active migrants and asylum seekers from countries with an HIV prevalence of >1 % should be offered a full sexual health assessment, with test for syphilis, *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. Sexual health screenings should be offered to sexually active migrants and asylum seekers from countries with an HIV prevalence rate of ≤1 %, as appropriate for their sexual history. See Table 3 for recommendations.

3.9. Intestinal parasites

With regard to intestinal parasites, four GLs were selected [6,19,55,56]

The Canadian [55], Australian [19] and American [56] GLs recommend Strongyloides and Schistosoma screening of migrants and asylum seekers newly arriving from highly endemic countries (Southeast Asia and Africa for Strongyloides and Africa for Schistosoma). Symptoms search and the subsequent tests for intestinal parasites are recommended in three documents [6,19,55]. All selected GLs also underline that migrants and asylum seekers with eosinophilia should be tested for Strongyloides and Schistosoma, as eosinophilia is a possible marker of these two infections. Serology is recommended as the appropriate screening test [19,55] and stool microscopy in case of presence of symptoms and/or eosinophilia [6,19,56]. All the included literature agrees on the fact that positive patients have to be treated. See Table 3 for recommendations.

3.10. Diabetes

Based on the systematic literature search, four GLs were included in relation to diabetes [5,7,19,57].

ASID [19] and CDC [7] GLs recommend searching for signs and symptoms of the disease as soon as possible during the reception pathway. ASID [19] and Canadian Medical Association [5] GLs recommend glycaemia testing in persons aged ≥35 years and coming from high prevalence countries, or with specific risk factors. NICE [57] suggests to provide information on disease prevention through healthy eating and lifestyles, and on possible complications. See Table 3 for recommendations.

3.11. Anaemia

Based on the systematic literature search, four GLs were included in relation to anaemia [5,7,19,58].

ASID GL [19] and the two CDC documents [7,58] recommend evaluating any risk factor or sign and symptom of nutritional deficiency during medical anamnesis. The same documents recommend a blood count for all migrants and asylum seekers; regarding the blood count, the Canadian GL [5] recommends to restrict the blood count to women of reproductive age and to children aged 1–4 years). See Table 3 for recommendations.

3.12. Hypertension

Regarding hypertension, two GLs were selected [7,19].

Both ASID [19] and CDC [7] recommend checking for hypertension in newly arrived migrants; pressure control is restricted to migrant aged ≥18 years in CDC document [7]. See Table 3 for recommendations.

3.13. Pregnancy

Only ASID [19] gives recommendations on ascertaining pregnancy in newly arrived migrants and asylum seekers. The GL recommends evaluating the possible pregnancy status in women of fertile age and offering them the test, if appropriate. In addition, pre-natal and perinatal care must be guaranteed to pregnant women by female health personnel and cultural mediators, in line with the protocols of the Australian Health System. See Table 3 for recommendations.

3.14. Cervical cancer

Three GLs were selected in relation to cervical cancer [5,7,19].

All three documents recommend offering screening for cervical cancer through Papanicolaou test to migrant and asylum seeker women: Australian and the Canadian GLs [5,19] restrict screening to sexually active women. CDC GL [7] stresses the importance of carrying out the screening within an appropriate and culturally sensitive context, since many women may have suffered sexual violence or experienced other traumatic events. See Table 3 for recommendations.

3.15. Vaccinations

Seven GLs [6,7,19,59–61] and one consensus conference [52] were included, based on the systematic review.

GLs from Australia (ASID and Australian Government) [19,59], American CDC [7], Ireland [6] and Canada [5] recommend a catch-up immunization strategy which takes into account previous vaccinations only if documented. In absence of valid documentation, immunization should be carried out according to the country vaccination schedule; serological tests are not considered as needed, with the exception of hepatitis B and rubella in women of reproductive age, in which it is appropriate to carry out an antibody titre (ASID also recommends chickenpox test for people aged >14 years). The New Zealand GL [60] recommends HBV vaccination for non-immune, and chickenpox, measles, mumps and rubella (MMR) vaccinations; it additionally focuses on tuberculosis, recommending vaccination of children with risk conditions. NICE [61] recommends an initial assessment of the immunological status of migrants and asylum seekers arriving in the country, discussing with them or their parents (in the case of children) the possibility of any other vaccination. The Italian consensus conference [52] deals with prevention, diagnosis and treatment of hepatitis B and C: it recommends HBV screening and vaccination for migrants and asylum seekers at risk, including persons originating from high prevalence areas, drug addicts, partners of infected individuals and persons affected by chronic liver diseases. See Table 3 for recommendations.

3.16. Diversified approaches to diseases/conditions

For each question, the literature review pointed to effective approaches for timely identification of health needs: these approaches included active case finding (based on signs/symptoms of disease); testing offered to asymptomatic members of given groups; mass screening; or integration into routine national health services. The choice was based on epidemiological considerations (like the endemic level in the country of origin or exposure to specific risk factors), availability and sustainability of treatment/care and ethical consideration. In particular, active case finding of signs/symptoms of disease (symptomatic cases) is recommended for tuberculosis disease, malaria, sexually transmitted diseases, intestinal parasites, diabetes, anaemia and pregnancy. Testing (screening) should be offered to asymptomatic individuals coming from endemic areas or exposed to specific risk factors for the following conditions: latent TB infection, HIV, HBV, HCV, syphilis, chlamydia, gonorrhoea, strongyloides, schistosoma, diabetes. Mass screening of all asymptomatic migrants and asylum seekers is recommended for anaemia and hypertension. Cervical cancer screening and vaccination programs should be offered to migrants and asylum seekers after integration into the Italian Health System, through the same age-specific programs offered to the Italian population. For each considered infection/pathology/condition, the referral of the migrant or asylum seeker to the dedicated diagnostic-therapeutic path is recommended, if required.

Furthermore, during the whole reception pathway emphasis needs to be put on the linguistic and socio-relational dimension of care in the various intervention settings; therefore contents and

forms of messages should be adapted to migrants and asylum seekers' cultural reference systems. It is also necessary that social and health workers are adequately trained in a transcultural approach and receive adequate psychological support when dealing with emotionally stressful situations.

3.17. Continuity of care, prevention and health promotion across all reception phases

After drafting the recommendations, and for their easy implementation, each of them was located at the appropriate stage of the reception pathway (rescue at sea, first and second line reception): the aim was to propose continuity of care and guidance for the standardization of local protocols. Therefore, based on evidence of effectiveness and on opportunities provided by the setting, a modulated, progressive approach was proposed.

In particular, during the rescue phase the GL recommends a medical evaluation of signs and symptoms indicative of clinical conditions requiring urgent health assistance or care: as a consequence, it was deemed appropriate that during this phase attention is paid to signs and symptoms of conditions such as tuberculosis disease, malaria, ectoparasitosis, intestinal parasites, and anaemia.

During first line reception, medical examination takes place in a more protected context and with the availability of more time: therefore, it is possible to have a counselling session and evaluate personal and family medical history for chronic and/or infectious diseases, drug history, trauma. In addition, the search for signs and symptoms should be performed at this time, in order to identify the possible presence of tuberculosis disease, malaria, ectoparasitosis, sexually transmitted diseases, intestinal parasites, diabetes, anaemia and hypertension. In this phase pregnancy should be ascertained and pregnant women should be referred to the dedicated reception pathway.

During second line reception, the NHS takes charge of migrants and asylum seekers: as a consequence, at this stage they can be offered screening tests and vaccinations. In particular, an active investigation of diseases/infections (latent TB infection, HIV, HBV, HCV, syphilis, chlamydia, gonorrhoea, strongyloides, schistosoma, diabetes), even in subclinical forms, should be performed: specific screening procedures are offered to asymptomatic subjects, according to epidemiological criteria (high endemicity) and/or to the assessment of risk exposure. Primary prevention is provided to children through vaccinations, according to the national schedule; some vaccinations are also recommended for adults. Mass screening is recommended for complete blood count, and women aged 25–49 should be included in local cervical cancer screening programmes.

Table 4 summarizes GLs recommendations for timely and appropriate identification of health needs, locating them within the Italian reception pathway.

4. Discussion

The present GLs are conceived as a tool to be primarily offered to decision-makers, reception centres managing bodies and social and health workers. Its aim is to promote effective and appropriate health assessments on migrants and asylum seekers upon arrival in Italy and during the subsequent reception phases, in order to avoid uncertainty and variability of practices at regional and local level.

These GLs are, to the best of our knowledge, the first document produced on this important topic with this methodological rigour in Italy; in addition, similar documents are generally focused on infectious diseases, while the present GLs deal with a broader spectrum of conditions, addressed by a multidisciplinary panel including also civil society organizations. The originality of the document lies also on the fact that it provides a complete schedule for medical assessments tailored to the different phases of the Italian reception pathway. This implies that, for the same health condition, the recommended approach may differ according to the specific reception phase.

In addition to the assessments related to specific health conditions, the GLs stress that, at each phase of the pathway, any individual diagnosed with pathological conditions should be guaranteed access to a suitable treatment. Moreover, a constant relationship between health personnel and migrants and asylum seekers should be established in order to allow effective counselling on most frequent diseases, their risk factors and prevention measures. Healthcare workers should receive an adequate training on the epidemiological situation in migrants' countries of origin and transit, and on signs and symptoms of specific diseases (such as malaria or diabetes). Furthermore, they should be trained on a culturally competent approach, which takes into consideration patient's language proficiency and cultural system. At some occasions they should be assisted by interpreters and cultural mediators. They should also receive adequate psychological support in order to manage emotionally stressful situations and to avoid burnout. In this regard, although these GLs are focussed on newly arrived migrants and asylum seekers, their recommendations provide useful indications also for health personnel working with settled migrant communities.

A similar document, limited to infectious diseases, was published by ECDC in 2018 [11]. On most of the considered infectious diseases, the two documents recommend similar measures, except for tuberculosis and hepatitis C. With regard to tuberculosis, the present GLs suggest the use of x-ray only for symptomatic patients, whereas ECDC recommends, with low grade of evidence, to "offer active TB screening using chest x-ray soon after arrival for migrant populations from high-TB incidence Countries". In fact, most supporting literature considers a pre-entry screening approach: this is applicable to many developed countries but not to Italy, where the majority of migrants and asylum seekers arrives outside planned flows, with costs of health screenings being borne by the NHS. Furthermore, Italian epidemiological data show a low prevalence of active tuberculosis among newly-arrived migrants and an increased incidence after the first 2 years of stay, which makes mass screening poorly cost-effective [29,[62–64]. With regard to hepatitis C, the Italian GLs recommend testing for people coming from countries with a prevalence rate higher than 3 %; while ECDC is more restrictive, using 2 % as cut-off line for testing. The two documents adopt similar ethical approaches, recommending that any screening and vaccination should be voluntary, confidential, non-stigmatising and performed for the benefit of the patient; screening procedures must be followed by care and treatment, when requested. Moreover, both documents recommend the removal of individual, community and health system barriers, so that migrants can have full access to screening, vaccination and treatment.

4.1. Implementation and implications for healthcare services

For the GLs to be fully effective, their recommendations have to be implemented on the ground, overcoming structural and organizational barriers that are often source of social and geographical health inequalities. A specific barrier to implementation in Italy is due to the decentralization of the Italian Public Health System that took place in the framework of a constitutional reform that led to the shift of many competences, including health, from the central State to the Regions, since 2001: this often creates an uneven application of national indications and of guidelines, also in the case of migrants' health [66]. As a preliminary step in the implementation process, therefore, and in consideration of the fact that State

Table 4
Early identification of health needs during the reception pathway: summary chart.

	RESCUE AND INITIAL CARE	FIRST RECEPTION	SECOND RECEPTION
Purpose of health assessment	**Initial medical evaluation:** presence of signs and symptoms indicative of clinical conditions requiring emergency/urgent care	**Medical examination:** medical history and active search for signs and/or symptoms indicative of specific diseases	**Registration with the Italian National Health Service:** primary prevention (vaccinations) and secondary prevention, including active detection of diseases, even in subclinical forms, through specific screening procedures
Medical history		Personal and family **medical history** of chronic and/or infectious diseases, drug history, trauma, pregnancy	
			Presence of risk factors for HIV, HBV, HCV, STI (past transfusions, TD, multiple sexual partners, sexual abuse, accidental contact)
Clinical examination	**Detection of signs and/or symptoms**: • cough lasting for ≥2 weeks (TB) • fever, splenomegaly (malaria) • skin inspection (ectoparasitosis) • diarrhoea, abdominal pain, nausea, vomiting, itching • signs and/or symptoms of anaemia	**Detection of signs and/or symptoms**: • cough lasting for ≥2 weeks (TB) • fever, splenomegaly (malaria) • skin inspection for the identification of ectoparasitosis • vaginal, cervical or urethral secretions, dysuria, genital and oral ulcers, skin rash, inguinal lymphadenopathy (STIs) • diarrhoea, abdominal pain, nausea, vomiting, itching, current or past haematuria (parasitosis) • signs and/or symptoms of diabetes • signs and/or symptoms of anaemia • blood pressure measurement	
Screening tests			**Screening:** • complete blood count for all migrants and asylum seekers • inclusion of women aged 25–49 in local cervical cancer screening programmes **Epidemiological criteria (high endemicity) and/or exposure to risk factors:** • TST/IGRA for asymptomatic migrants and asylum seekers from countries with TB incidence >100/100,000 • HIV test for migrants and asylum seekers aged ≥16 years and coming from countries with prevalence >1 %; for pregnant or breastfeeding women; and for persons (including children) exposed to risk factors or with co-infections (other STIs or TB) • HBsAg, HBcAb and HBsAb serology for migrants and asylum seekers coming from countries with HBV prevalence >2 %, and/or with risk factors, or pregnant women • HCV test for migrants and asylum seekers coming from countries with prevalence >3 % and/or persons with risk factors • diagnostic tests for Chlamydia trachomatis and Neisseria gonorrhoeae infections, based on PCR test from urine or on cervicovaginal swabs of asymptomatic persons with STI risk factors • syphilis serology for persons aged ≥16 years, coming from high HIV-endemic areas and/or exposed to risk factors; for minors <16 years with individual risk factors or with other STIs • *Strongyloides stercoralis* and *Schistosoma spp* serology for migrants and asylum seekers having lived or travelled in endemic areas • fasting blood glucose for migrants and asylum seekers aged ≥35 years, coming from countries with high diabetes prevalence and with specific risk factors
Vaccinations			**Unvaccinated children (0–14 years) or those with uncertain or unknown vaccination status** Vaccinations as from the national schedule in force, and according to their age **Adults with uncertain or no vaccination history:** • polio • measles, mumps, rubella, chickenpox, excluding pregnant women • diphtheria, tetanus, pertussis • HBV for the entire adult population screened and negative for serological markers

and Regions share legislative competence on health, the Permanent Conference for Relations between the State, the Regions and the Autonomous Provinces of Trento and Bolzano approved the GLs as National Italian Guidelines in May 2018 [65]. Subsequent, government changes, bringing different political approaches to migration and reception and the related legislative modifications, did not fully support a comprehensive implementation strategy at national level. Noteworthy, however, is that during 2018–2020 the Ministry of Health promoted and implemented the national project "Footprints" (Training of Public Health personnel for the definition of Regional Coordination Plans for Migrants' Health, and the creation of a community of practice) [67] aimed at strengthening regional coordination systems for migrants' health and pushed for GLs implementation across Italian Regions.

At regional level, transposition of the approved National GLs into a regional act would add force to their recommendations, by giving the occasion to adapt the national protocols to the regional health system: some Regions produced specific contextualization acts just before (Marche, Sicily, Sardinia Regions) and after (Lazio and Tuscany Regions) the formal approval of the GLs, introducing implementation monitoring mechanisms in some cases. The Italian Society of Migration Medicine launched a monitoring exercise looking, among other items, also at how the GLs have been transposed at regional level (initial results awaited in December 2020).

A limit to the applicability of these GLs lies in the dynamics of the migratory phenomenon, which entail ongoing reviews: for example, the burden of different conditions considered in countries of origin of migrants and asylum seekers may rapidly change. The need for frequent updates is also due to possible modifications and improvements in diagnostics, with a consequent evolution of the related literature.

In conclusion we suggest that GLs, in addition to be based on a systematic literature review in order to identify evidence-based, effective and appropriate health assessments for migrants upon their arrival and while hosted in reception centres, should additionally consider a targeted approach for each health condition, based on the country of origin and transit or on exposure to specific risk factors; on the availability and sustainability of treatment/care; and on ethical considerations related to the screening procedures (i.e. be voluntary, confidential and non-stigmatizing). We recommend also that each health assessment be related to a specific phase of the reception pathway, in order to avoid unnecessarily repeated assessments and to guarantee effective prevention and continuity of care.

Finally, the following "*take home messages*" can be addressed to policy-makers:

- it is important to produce and periodically update GLs on these issues (research dimension);
- it is essential to disseminate and implement these guidelines taking into account the organizational and management peculiarities of local health services (management dimension of health services);
- GLs have to be supported by training programs targeting health professionals in order to increase their clinical and cultural competence (dimension of welfare quality);
- tools such as these GLs are useful not only to improve clinical appropriateness of interventions, but also to promote economic sustainability and to counter stigmatization and discrimination dynamics (social impact dimension).

Author statement

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Declaration of Competing Interest

The authors report no declarations of interest.

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Appendix A. Supplementary data

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CHAPTER 4 – ASSESSING THE BURDEN OF NTDS AND OTHER INFECTIONS IN A LARGE COHORT OF AFRICAN REFUGEES AND ASYLUM SEEKERS

Manuscript in preparation for submission

Screening for Neglected Tropical Diseases and other infections in African refugees and asylum seekers in Rome and Lazio region, Italy

Marrone R, Mazzi C, Ouattara H, Formenti F, Mirisola C, Perandin F, Bisoffi

Abstract

Background

Few reliable data are available on Neglected Tropical Diseases (NTDs) and other infections among African refugees and asylum seekers in Italy.

We aimed to estimate the prevalence of NTDs and other infections in a large cohort of African refugees and asylum seekers living in reception centers in Lazio, Italy.

Material and Methods

This is an observational, prospective prevalence study on infectious diseases in a large population of African refugees and asylum seekers consecutively enrolled for screening purpose at the Infectious and Tropical diseases outpatient clinic of the National Institute of Migrant and Poverty (INMP), Rome from August 2019 to December 2020.

Results

We found a prevalence of 8.8% and 31% for *Strongyloides* and schistosoma infection, respectively, while the prevalence of human immunodeficiency virus (HIV) infection was 0.7%, HCV antibodies 2.5 %, hepatitis B virus surface antigen 10.8% and syphilis serological tests 2.9%.

Conclusion

Strongyloidiasis and schistosomiasis are highly prevalent among African refugees and asylum seekers in Italy, in contrast to communicable diseases (with the exception of hepatitis B).

Raising awareness of NTDs among health professionals and implementing guidelines seems to be of paramount importance to prevent these diseases and their sufferers from becoming even more

"neglected".

Keywords: Schistosomiasis, strongyloidiasis, NTD, refugees, asylum seekers, infectious disease screening, HIV, syphilis, HCV, HBsAg.

Introduction

Over 128 000 irregular arrivals of migrants coming mainly from African and Asian countries to Europe via the Mediterranean migration routes were recorded in 2019 (1).

Although more than 85% of international refugees are actually hosted in developing countries (2), since the beginning of 2015, more than one million people have crossed the Mediterranean Sea risking their lives to reach Europe.

Due to its geographical position in the Mediterranean Sea, Italy, is one of the main landing countries of migrants coming from Libya and Turkey. The estimated number of asylum seekers in 2019 was 43,783 with the 81% of the asylum requests denied and the number of people that live illegally in our territory still unclear.

Asylum seekers and refugees differ from other migrants, as they have not chosen to migrate but rather have been forced to flee their country, family, community, culture and job (3).

They are mostly young healthy individuals but when they arrive in Europe, they are often traumatized by the violence they have suffered, both physically and mentally, during the migratory journey (4). African asylum seekers and refugees have been described as carrying significant infectious disease burden, related to the epidemiological picture in the country of origin as well as across the migratory route and in the country of destination (5, 6). They can suffer from infections with worldwide distribution (such as tuberculosis or human immunodeficiency virus) or tropical infectious diseases typical of their areas of origins that can be asymptomatic for long periods of time (7,8) but ultimately cause a significant mortality burden (9). Migration may modify the epidemiology of certain infectious diseases in the world introducing new infections that in the presence of a viable vector could produce outbreaks in the host country or reintroducing previously eradicated infections (10, 11). So the incidence of certain globally distributed infections may be changed and may increase in the host countries despite autochthonous cases declining (12).

The objectives of this study were to estimate the prevalence of selected infectious diseases, both communicable and non-communicable, in a cohort of symptomatic and asymptomatic African migrants and asylum seekers, in order to assess the burden of latent infections with a potential for significant complications and mortality risk.

Material and Methods Ethics statement

This study was approved by the Ethical committee of the Italian Higher Institute of Health (Istituto Superiore di Sanità—PRE-712/16) on 30 July 2019. Informed consent was obtained from all subjects involved in the study. Legal guardians' consent was obtained for unaccompanied minor migrants aged less than 18 years.

Type of study

Observational, prospective prevalence study. This is a study of infectious diseases screening in a population of African refugee and asylum seekers arrived in Italy, recently and temporarily residing in reception centers in Lazio, Italy.

The study was conducted on individuals accessing the Infectious and Tropical diseases outpatient clinic of the National Institute of Migrant and Poverty (INMP), Rome from August 2019 to December 2020. Subjects were consecutively enrolled for screening purpose, regardless the presence/absence of symptoms/signs.

Subjects

African refugees and asylum seekers were recruited upon their arrival at the reception centers in Lazio. All of those included in the study underwent a complete medical examination and infectious disease screening according to Italian and European guidelines (13, 14).

A cultural mediator was also present during the clinical activity in order to facilitate and strengthen the relationship between the migrants and the health personnel. When necessary, patients were referred to infectious disease departments for further investigation or hospitalization as the INMP only provides out-patient care.

Inclusion criteria: subjects of all ages, refugees and asylum seekers, with signed written consent form for the participation to the study and for the donation of biological samples for study purpose. Both consent forms were also signed by guardians in case of unaccompanied minors.

Exclusion criteria: lack of signed written informed consent, including to the use of biological specimens for the study purpose.

Diagnostic tests

All subjects registered with the Italian National Health System were tested for full blood cell count

(FBC), total class E immunoglobulins (total IgE), antibodies anti human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), anti-hepatitis B surface (HBs) antibodies, anti-hepatitis B core (HBc) antibodies anti-hepatitis C virus (HCV) antibodies. All assays for HBV and HCV were detected with ELISA (Beckman Coulter, Inc.).

Antibodies anti human immunodeficiency virus (HIV) were performed with an ELISA (Beckman Coulter, Inc.), and a Western blot (Fujirebio Diagnostics) used as confirmatory test. Anti-HBs and anti-HBc antibodies were detected by commercial immunoassay methods following the manufacturer protocols. HBsAg was detected by electrochemiluminescence immunoassay (ECLIA) and anti-HCV antibodies by enzyme-linked immunosorbent assay (ELISA). Screening for syphilis was performed by a reverse syphilis test algorithm, which starts with an assay to measure specific IgM and IgG antibodies to *Treponema pallidum* (*T. pallidum*) (TPA). If TPA screen was reactive, samples were tested for rapid plasma reagin to assess disease activity. If this test was negative, the sample was tested for a second *T. pallidum*-specific test–*T. pallidum* particle agglutination, TP-PA–to confirm the initial TPA screen.

Schistosomiasis was diagnosed using stool and urine microscopy (for ova) and qPCR as well as serology (Schistosoma mansoni ELISA kit, Bordier Affinity Products SA, Crissier, Switzerland), Western Blot (WB IgG containing both antigens species (SCHISTO II WB IgG, LDBIO, France), and a rapid diagnostic test (RDT): Schistosoma ICT IgG-IgM (SCHISTOSOMA ICT IgG-IgM, LDBIO, France). Strongyloidiasis was diagnosed using stool qPCR and microscopy, a commercial ELISA (Bordier ELISA -Bordier Affinity Products, Switzerland-for *S. stercoralis*) and an in-house immunofluorescence test (IFAT). Protozoa and other helminths were diagnosed by parasitological and molecular examination of faeces.

All biological samples (blood, urine, stool) were collected at the INMP where Schistosoma ICT and urine microscopy were performed, while blood aliquots were sent to the laboratory of San Camillo hospital, Rome, for the full blood count, total IgE, and HIV, HBV, HCV, syphilis screening. Other samples were sent to the Department of Infectious and Tropical Diseases and Microbiology (DITM), IRCCS Sacro Cuore Don Calabria Hospital in Negrar, Verona, to perform helminth and protozoa screening tests.

All positive individuals at any screening test were referred to the INMP specialists on infectious diseases for the appropriate clinical management and active immunization was offered to subjects who were susceptible to HBV infection.

The results were then anonymously entered in an Excel database.

Composite reference standard (CRS) for schistosoma and S. stercoralis infection

Although screening for schistosomiasis and strongyloidiasis has been formally included in Italian and European guidelines (13, 14), there is no diagnostic gold standard for either infection. The reason is that the direct tests (looking for schistosoma eggs in stools or urine or for *Strongyloides* larvae in stools, Figure 1 and 2) are poorly sensitive, and so is the search for parasitic DNA in both stools and urine with PCR. Of course, the specificity of both methods is 100%. For this reason, the guidelines indicate serology as the preferred screening test, as it has been found to be a highly sensitive method. However, serologic tests may provide a variable proportion of false positive results, due to cross reactions with other parasites or to the presence of antibodies as a result of past infections.

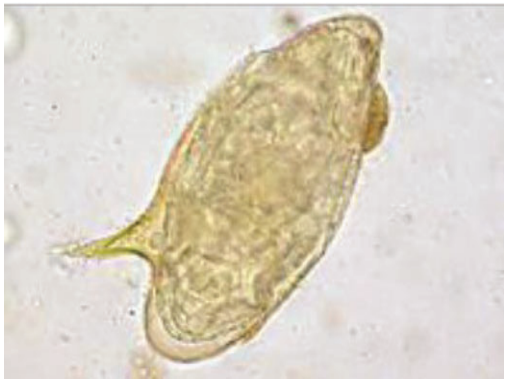

Figure 1 – Egg of *Schistosoma mansoni* in stools (photo DITM – IRCCS SCDC Negrar)

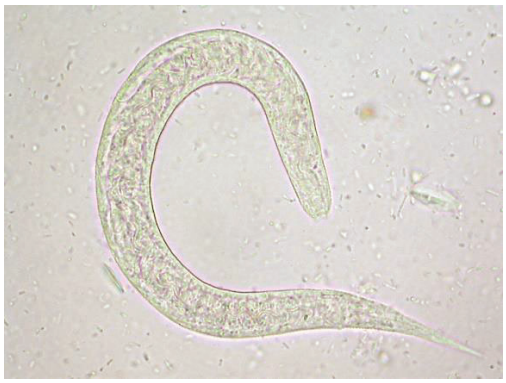

Figure 2 – Larva of *Strongyloides stercoralis* in stools (photo DITM – IRCCS SCDC Negrar)

One of the methods indicated to cope with the lack of a gold standard is the compositive reference standard (CRS), based on combination of tests (15, 16).

For strongyloidiasis, the CRS is based on the combination of the results of ELISA, IFAT, fecal microscopy and fecal PCR. Based on previous diagnostic studies, (17) the ELISA test used has a very good specificity, but a less good sensitivity. On the other hand, the IFAT test (an in-house test developed at DITM) is virtually 100% sensitive (but poorly specific) at the lower titres of ≤1/80, while is virtually 100% specific at titre >1/80. (18,19) Thus, the CRS for *S. stercoralis* infection is defined as follows: Infected if AT LEAST one between: microscopy, RT-PCR, ELISA test, and IFAT>1/80 is positive; not infected when all tests are negative; undetermined if only IFAT is positive at a lower titre.

For schistosomiasis, the CRS is also structured on the combination of the results of serological tests (WB, ICT and ELISA) and, again, microscopy and RT-PCR. According to the CRS, a subject is classified as infected if a) microscopy and/or RT PCR is positive; OR b) at least two of the three

serological tests are concordant positive; not infected when all tests are negative; undetermined if only one of the serological tests is positive.

Statistical analysis

Continuous variables were summarised with medians and interquartile ranges, while categorical variables were summarised with absolute and percentage frequencies. The chi-squared or Fisher exact test was used to test associations between categorical variables. A multivariable logistic regression model was used to explore the associations between Schistosoma/Strongyloides positivity and several regressors: abdominal pain, pruritus, urinary pain (only for Schistosoma infection), IgE positivity and eosinophilia. Models were run excluding indeterminate cases at CRS. Estimates were reported with 95% CIs and a p-value < .05 was considered to indicate a statistically significant difference.

Results

Data from 936 African refugee and asylum seekers immigrants were analyzed**.** In this study group, 80.1 % (750) were male, and median age was 26 years.
The most frequent countries of origin were: Nigeria (23%), Ivory Coast (13.5%), Mali (11.8%), Senegal (10.5%), Gambia (10%), Guinea (8.6%), Ghana (4.3%) and others (18.4%).

Helminth infections

A special focus was on the two helminth infections specifically targeted by both European and Italian guidelines: *S. stercoralis* and schistosoma.

S stercoralis

A stool sample was provided and analyzed in 928 of the cases by microscopy and in 925 of the cases by qPCR. The former was positive for 25 subjects (2.7%), while qPCR in was positive for 27 subjects (2.9%). Screening with *S. stercoralis* serology was done for 934 individuals, 68 (7.3 %) of whom were positive to ELISA and 44 (4.7%) to IFAT test, titre >1/80.
IFAT serology at lower titre was positive for 275 subjects (29.4%).
Table 1 shows the number of subjects tested, the different methods used for the diagnosis of strongyloidiasis and the respective results.

Table 1 – Diagnostic method for strongiloidiasis

DIAGNOSTIC METHOD	N subjects tested	Positive results
	N=	N = (%)
ELISA	934	68 (7.3%)
IFAT >1/80	934	44 (4.7%)
Stool microscopy	928	25 (2.7%)
Stool qPCR	925	27 (2.9%)
CRS	926	81 (8.8%)

The proportion of positive results according to the CRS was 8.8% (81/926).

Of the 81 subjects with strongyloidiasis at CRS, 77 were also tested for HTLV1 infection (ELISA), of whom 3 (4%) were positive.

Table 2 reports the detail of strongyloidiasis (CRS) prevalence (according to CRS) by country.

Table 2 – Stratification of strongyloidiasis positives by country

COUNTRY	Positive subjects
	N (%)
Nigeria	18/215 (8.4%)
Guinea Conakry	13/80 (16.2%)
Ivory Coast	12/123 (9.8%)
Mali	10/110 (9.1%)
Other	28/398 (7.0%)

Schistosoma

Results of the different tests for schistosoma are summarized in Table 3.

Table 3 – Diagnostic method for schistosomiasis diagnosis

DIAGNOSTIC METHOD	N subjects tested	Results
		N (%)
ELISA	934	220 (23.6%)
WB	934	304 (32.5%)
ICT	913	282 (30.9%)
Micro stool	928	86 (9.3%)
Micro urine	768	13 (1.7%)
qPCR stool	925	91 (9.8%)
qPCR urine	548	12 (2.2%)
CRS	903	280 (31%)

Of 928 individuals tested with faecal microscopy, 86 (9.3%) were positive for *S. mansoni* and 3

(0.3%) for *S. haematobium* (no positive for both species). Urine microscopy was tested in 768 individuals, and 13 (1.7%) presented *S. haematobium* eggs.

Concerning Real Time PCR (qPCR) on stool samples, over 925 tested, 91 (9.8%) were positive, and so were 12 (2.2%) of 548 subjects tested on urinary samples.

At serology, ELISA was positive in 220 subjects (23.6%), WB in 304 (32.5%), ICT in 282(30.9%).

The proportion of positive results according to the CRS was 31% (280/903). NB CRS was calculated on subjects having the available results of all the relevant tests.

Species-specific results of microscopy for *S. mansoni* and *S. haematobium* are summarized in Table 4.

Table 4 – Microscopy results for *S. mansoni* and *S. haematobium*

	S. mansoni		
S.haematobium	Negative	Positive	Total
Positive	13 (86.7)	2 (13.3%)	15 (100%)
Negative	829 (90.8%)	84 (9.2%)	913 (100%)
Total	842 (90.7%)	86 (9.3%)	928 (100%)

Considering both stool and urine microscopy (the latter specific for *S. haematobium*, the former for *S. mansoni* but with the occasional finding of ectopic *S. haematobium* eggs), we have 84 (9.2%) subjects positive for *S. mansoni* only, 13 (1.7%) positive for *S. haematobium* only, and only 2 (0.2%) for both species. Thus, a total of 99 subjects (10.7%) had schistosoma eggs found at microscopy of stool and/or urine.

Schistosomiasis screening was performed on migrants from 29 African countries: Mali, Ivory Coast, Senegal and Guinea Conakry had the highest prevalence.

Table 5 reports the detail of schistosoma prevalence (according to CRS) by country.

Table 5 – Stratification of Schistosoma infection by country

COUNTRY	Subjects
	N (%)
Mali	70 /110 (63.6%)
Ivory Coast	53/123 (43.1%)
Guinea Conakry	39/80 (48.8%)
Senegal	29/93 (31.2%)
Other	89/497 (17.9%)

Only 23/936 subjects (2.5 %) stated that they were aware of schistosomiasis. Only among migrants from Egypt did 53.8% say they were aware of the disease because they had been involved in control programmes in their country.

Other infections

The results of screening for communicable infections is resumed in Table 6.

Table 6 – Screening syphilis, hepatitis B, C , HIV results

Test	*Negative*	*Positive*	*Total*
Syphilis	760 (97.1%)	23 (2.9%)	783 (100%)
HBV (HBsAg+)	704 (9.2%)	85 (10.8%)	789 (100%)
HCV (HCV Ab)	763 (97.5%)	20 (2.5%)	783 (100%)
HIV	747 (99.3%)	5 (0.7%)	752 (100%)

*The percentages have been calculated as number of cases divided by number of patients in whom the test was performed in each group.

Briefly, 5 of 752 individuals (0.7%) screened were positive for HIV infection, 85 of 789 (10.8%) for HBsAg, 68 of 789 (8.6%) were vaccinated for hepatitis B (HBsAg-, HBsAb + HBcAb-), 20 of 783 (2.5%) for anti-HCV test (of whom only 2, or 10%, were positive at HCV PCR). *Treponema pallidum* serology was performed for 783 subject and was positive in 23 (2.9%).

Schistosoma and hepatitis B coinfection

Of 794 migrants screened for both schistosomiasis and hepatitis B, 85 (10.7%) were HBsAg.positive. In particular, 39 of the 258 schistosoma positive subjects (15.1%) were HBsAg positive, versus 40/454 (8.8%) of schistosoma negative and 6/70 (8.6%) of schistosoma indeterminate results (p=0.0277).

Table 7 shows the results of Schistosoma and HBsAg positive subjects.

Table 7 – Correlation between Schistosoma infection (according to CRS) and HBsAg

	HBsAg		
Schistosoma (CRS)	Positive	Negative	Total
Positive	39 (15.1%)	219 (84.9%)	258 (100%)
Indeterminate	6 (8.6%)	64 (91.4%)	70 (100%)
Negative	40 (8.8%)	414 (91.2%)	454 (100%)
Total	85 (10.9%)	697 (89.1%)	782 (100%)

In the whole cohort, eosinophilia (eosinophil count > 400/ μL) was present in 19.5% (160/820) the median eosinophil count was 49/μL (IQR: 35.8 - 68.2),). The median of total IgE levels was 139 (IQR: 79 - 220), and overall they were elevated in 55.2% of patients (160/820).

387 subjects were asymptomatic (41.3%) and 549 symptomatic (58.7%) of which 15 % (141/936) subjects reported suffering from genitourinary disorders (in the schistosomiasis group alone), 42.7% (430/936) from gastrointestinal complaints, and 58.6% (549/936) from itching.

Clinical manifestations, eosinophilia and total IgE in migrants with strongyloidiasis or schistosomiasis.

The prevalence of gastrointestinal symptoms was 66.7% among those positive for strongiloidiasis, 58.5% among the indeterminate group and 38.2% among those without strongiloidiasis. Itching was reported by 75.3% of patients with strongyloidiasis and by 61.4% and 30.7% of migrants with an indeterminate or negative diagnostic test, respectively. Eosinophilia was present in 58.6% of cases and a high total IgE in 81.6% (Table 8).

Table 8 – Clinical manifestations, IgE tot and eosinophilia in migrants with strongiloidiasis

SYMPTOMS	Positive	Indeterminate	Negative	P-value
Gastrointestinal symptoms	66.7% (54/81)	58.5% (144/246)	38.2% (229/599)	<0.001
Pruritus	75.3% (61/81)	61.4% (151/246)	30.7% (184/599)	<0.001
Total IgE	81.6% (40/49)	55.2% (100/181)	52.5% (224/427)	0.002
Eosinophilia	58.6% (41/70)	17.9% (32/207)	15.3% (82/536)	<0.001

All these variables resulted significantly associated with the infection.

As for schistosomiasis, gastrointestinal symptoms were present in 81.4% of those positive for infection, 51.9% among those with indeterminate results and 38.2% among not infected. Itching was reported by 68.6% of patients with schistosomiasis and by 49.4% and 28.7% of migrants with indeterminate or negative results, respectively. Genito-urinary symptoms (active or reported) were present in 40.7% of patients with schistosomiasis and by 11.4% and 3.1% of those with indeterminate or negative results, respectively. Eosinophilia was present in 32.3% of cases and a high total IgE in 74.6% (Table 9).

Table 9 – Clinical manifestations in migrants with schistosomiasis

SYMPTOMS	Positive	Indeterminate	Negative	P-value
Gastrointestinal symptoms	81.4% (228/280)	51.9% (41/79)	38.2% (150/544)	<0.001
Pruritus	68.6% (192/280)	49.4% (39/79)	28.7% (156/544)	<0.001
Genito-urinary symptoms	40.7% (114/280)	11.4% (9/79)	3.1% (17/544)	<0.001
Total IgE	74.6% (150/201)	47.5% (28/29)	46.9% (186/397)	<0.001
Eosinophilia	32.3% (85/263)	11.1% (8/72)	14% (64/478)	<0.001

All these variables resulted significantly associated with the infection.

At multivariate analysis (logistic regression), of the named variables only pruritus and eosinophilia remained significantly associated with the diagnosis of strongyloidiasis (Table 10).

Table 10 – Results of logistic regression for *Strongyloides stercoralis* infection (selected characteristics)

Characteristic	N	Event N	OR1	95% CI1	P-value
Abdominal pain	469	47	1.07	0.48, 2.37	0.9
Pruritus	469	47	5.63	2.43, 14.2	<0.001
Total IgE	469	47	1.86	0.80, 4.66	0.2
Eosinophilia	469	47	4.84	2.41, 9.93	<0.001

1 OR = Odds Ratio, CI = Confidence Interval

For schistosomiasis, the multivariate analysis confirmed the significant association with the diagnosis for the variables considered, with the exception of eosinophilia (Table n.11).

Table 11 – Results of logistic regression for schistosoma infection (selected characteristics)

Characteristic	N	Event N	OR1	95% CI1	P-value
Abdominal pain	589	200	6.68	4.11, 11.1	<0.001
Pruritus	589	200	1.81	1.12, 2.92	0.016
Urinary symptoms	589	200	10.8	5.48, 23.0	<0.001
Total IgE	589	200	2.64	1.63, 4.31	<0.001
Eosinophilia	589	200	1.42	0.82, 2.47	0.2

1 OR = Odds Ratio, CI = Confidence Interval

Discussion

The aim of this study was to describe the prevalence of selected, chronic infections in African refugees and asylum seekers living in reception centers for migrants in Lazio, Italy and estimate the burden of latent infections potentially harmful for the health of the individual and potentially transmissible to the community.

This is the largest case series on infectious and parasitic diseases of African asylum seekers in Europe. Screening was carried out in 2019 and 2020, with a special focus on those infections that are targeted for screening by both Italian and European guidelines.

Similarly to other studies (20) we found that in individuals from sub-Saharan Africa the non-communicable helminth infections (and in particular the two targeted by guidelines: strongyloidiasis and schistosomiasis) are far more common than sexually transmitted infections, confirming that the concerns about the spread of the latter by migrants to the local population are unfounded.

We found 8.8% and 31% prevalence for *Strongyloides* and schistosoma infection, respectively, in our cohort. Both figures are higher than those reported in a previous Italian survey that had found a prevalence of 4.5 and 6%, respectively (21).

For both infections, it is well known that traditional microscopy on feces (and on urine for *S. haematobium*) have low sensitivity, thus, while they are obviously 100% specific in a qualified laboratory, they cannot be used alone for screening. In fact, guidelines recommend serologic screening for both. (13, 14). However, there are several serologic tests available, and the guidelines do not indicate the methods of choice.

To estimate the prevalence of both infections, we used a Composite Reference Standard (CRS), as explained in Methods.

The study confirms a high prevalence of strongyloidiasis, about 9%, but with a much higher number of suspected cases (indeterminate result based on CRS). All of these cases, including indeterminate (i.e., positive only by low titre IFAT test), were treated with ivermectin. The rationale is that it is preferable to treat a false positive (with a very well-tolerated drug) than to leave a false negative untreated. Incidentally, we should note that ivermectin has only very recently been registered in Italy, unfortunately at a not inconsiderable cost that still makes its massive use difficult for patients who need it.

Particular attention should be paid to the association between *S stercoralis* and HTLV-1, as different studies have shown that the coinfection modifies the immunological responses against parasite antigens and may result in an increase of the disseminated forms of strongyloidiasis as well as of recurrent infection. (22, 23). In our series 4% of patients with strongyloidiasis had HTLV-1

infection, too.

The prevalence of schistosomiasis was found to be very high. In particular, subjects from some West African countries were found to have a very high risk of schistosomiasis, peaking in people from Mali, Guinea and Ivory Coast. Surprisingly, almost no one was aware of this parasitosis, except for subjects from Egypt, more than half of whom reported knowledge of control programs in their country. Our prevalence data confirm a previous Italian report (24) that found 34% prevalence, peaking in subjects from Mali and Ivory Coast. In other studies, the prevalence was lower, ranging from 9 to 15% if based on use of microscopy (25, 26) and from 5.8 to 24.7% if based on ELISA serology (27, 28). Of course, these data should be considered with caution, as they may not be representative of the general population and because those that are based on relatively insensitive tests under represent infections with low parasite loads. (29) Urine and stool microscopy is 100% specific, but the sensitivity varies with the number of specimens collected, the intensity of infection, and the circadian and day-to-day variation of egg counts in stool and/or urine (30,31). The diagnosis of schistosomiasis by detection of specific antibodies is more sensitive than microscopy, particularly in light infections (32). In a study conducted by Beltrame et al. (33) rapid test ICT and Western Blot showed the highest sensitivity according to both composite reference standard (CRS) and Latent Class Analysis (LCA) model, suggesting that ICT could be used as a single screening test for migrants**.** Our study reiterates that thousands of people with this parasite are in our country and should be treated, or else face serious risks of clinical complications over time. Yet, the cases actually identified and treated are only a small minority. Moreover, the drug of choice, praziquantel, is not available in Italy and must be imported from abroad.

An innovative aspect of our study, made possible by the longitudinal design, is the statistical association of selected characteristics with the diagnosis of strongyloidiasis and schistosomiasis, respectively (Tables 8 to 11). Regarding strongyloidiasis, at univariate analysis, pruritus and abdominal pain were found to be strongly associated with infection, and so were eosinophilia and total IgE. However, based on logistic regression, this association is only confirmed for pruritus and eosinophilia. For schistosomiasis, a highly significant correlation was found at univariate analysis with pruritus, abdominal pain, genitourinary symptoms, eosinophilia and total IgE. This correlation was also confirmed at multivariate analysis for all variables considered except eosinophilia.

Regarding hepatitis B and C, our results do not differ much from what is reported in the literature, reporting a very low prevalence of HCV and a high prevalence of HbsAg positivity. The latter mainly reflects the still high risk of maternal-fetal transmission in countries of origin, rather than the risk of sexual transmission, also given the low prevalence of HIV and syphilis.

Also of note is the apparent correlation between hepatitis B and schistosomiasis, already reported by

other authors, that is, between two infections that both have the liver as their target organ. A previous study conducted by Marchese et al (34) reported 15.4% coinfection in a cohort of immigrants but found that schistosomiasis does not increase the risk of liver damage in people with HBV infection, contrarily to other studies (35, 36) that suggest a higher risk of chronic liver inflammation. Even if different studies showed that the prevalence of HBV in schistosomiasis patients is higher than in non-schistosomiasis patients and that the prevalence of HBV in highly-endemic areas of schistosomiasis is higher than in low-endemic areas, (37-38) the causal relationship is not clear, also because serologic testing for schistosomiasis cannot accurately distinguish between active and past infections (39). The low rate of Hepatitis B vaccination (8.6%), as has been found by other studies (40-42), suggests that dedicated programs should be implemented.

In accordance with other studies on adult and minor migrants (20, 42, 43), the prevalence in particular of hepatitis C, HIV and syphilis was very low, and a systematic screening may be questionable.

A limitation of this study is related to the characteristics of the population examined. Being almost completely composed of males, possible sex-related differences in the risk distribution of the considered infections was not assessed. Not all patients performed all the planned screening tests, either because of cultural barriers or for other reasons.

Using a CRS to classify cases of *S. stercoralis* and schistosoma infection is still an imperfect method, and a misclassification of some cases cannot be ruled out. However, only relying on direct methods would lead to a large underestimation of the true prevalence.

The main strengths of our study are the longitudinal design and the recruitment strategy, based on the screening of all subjects hosted in the shelters, regardless of the presence or absence of symptoms. The collection of clinical information was carried out independently of laboratory analysis, conferring a greater value to the correlations found.

Conclusions

The two NTDs targeted by the European and national screening guidelines, namely strongyloidiasis and schistosomiasis, are highly prevalent among African refugees and asylum seekers in Italy, in contrast to communicable diseases (with the exception of hepatitis B). Although these NTDs do not pose a risk to the Italian population, ethical principles should mandate full implementation of the guidelines, which instead are simply ignored in most cases.

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CHAPTER 5 – IMPROVING THE DIAGNOSIS OF STRONGYLOIDIASIS AND SCHISTOSOMIASIS

5.1 Strongyloidiasis: improving the diagnosis of "the most neglected of the neglected tropical diseases"

Strongyloidiasis is a parasitic infection caused by nematodes of the genus *Strongyloides*.

The global burden of the disease is underestimated due to lack of precise data from endemic countries but experts estimate that around 600 million people are affected worldwide. Almost all infections are caused by the species *S. stercoralis*, while rare human infections by *S. fuelleborni* have been reported in Africa and Asia (8). Almost all infections are caused by the species *S.stercoralis,* while rare human infections by S. *fuelleborni kellyi* appears to be restricted to the island of New Guinea. Some *S. stercoralis* strains can also infect non-human primates, cats and dogs, raising concerns about a possible zoonotic transmission.

The infection is transmitted through direct penetration of the skin by infective (filariform) larvae free-living in soil contaminated by human faeces. Thus, the transmission occurs in areas with inadequate sewage systems and hygienic conditions.

The health consequences of *S. stercoralis* infections range from asymptomatic light infections to chronic symptomatic strongyloidiasis. Uncontrolled multiplication of the parasite (hyperinfection) and potentially life-threatening dissemination of larvae to all internal organs is found among individuals with compromised immune system function.

Strongyloidiasis is considered by some the most neglected of the NTDs (9) because, until recently, it was not even included in the official list of NTDs according to the W.H.O., and therefore not included in control programmes.

The diagnosis of *S. stercoralis* infection is challenging because there isn't a gold standard test with optimal sensitivity and specificity. This makes it difficult to estimate the accuracy of new diagnostic tests.

In fact, if a novel test is compared with parasitological faecal examinations, which have very low sensitivity because of intermittent shedding of larvae, this may result in an overestimation of the sensitivity and an underestimation of the specificity. With this study, I applied the new skills acquired during my PhD training on how to assess a new test's accuracy when a gold standard is lacking.

Unfortunately, these methods are seldom applied, and almost never in parasitology studies, making it difficult to compare different studies.

Thus, with this paper, we achieved two main results: we assessed for the first time a new test for the screening of strongyloidiasis that was not yet commercially available, and we used the appropriate methodology for evaluating a new test in the absence of a gold standard.

microorganisms

MDPI

Communication

Prevalence of Strongyloidiasis in a Cohort of Migrants in Italy and Accuracy of a Novel ELISA Assay for *S. stercoralis* Infection, a Cross-Sectional Study

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Abstract: *Strongyloides stercoralis* infection is a life-threatening neglected tropical disease. Diagnostic issues have caused an underestimation of its global burden. The choice of appropriate diagnostic tests for the screening of populations at risk of the infection, such as migrants from endemic countries, is of paramount importance. From November 2017 to July 2018, all migrants presenting to the National Institute for Health Migration and Poverty (INMP) in Rome, Italy were offered screening tests for *S. stercoralis* infection. The study objective was to estimate the prevalence of strongyloidiasis in the study population and the accuracy of a novel ELISA assay. The following tests were carried out at the IRCCS Sacro Cuore Don Calabria hospital in Negrar, Verona: stool microscopy, real-time PCR for *S. stercoralis*, in-house immunofluorescence test (IFAT), a commercial ELISA assay (Bordier ELISA), and a novel ELISA assay (Euroimmun ELISA). A latent class analysis (LCA) model set up with test results, clinical variables, and eosinophilia indicated a prevalence around 7.5%, in line with previous findings. The sensitivity and the specificity of Euroimmun ELISA were 90.6% (95% CI 80.5–100) and 87.7% (95CI 84.5–91.0); these results indicate that the novel ELISA assay would be suitable for screening of migrants from endemic countries.

Keywords: *Strongyloides stercoralis*; strongyloidiasis; migrants; diagnostic tests; ELISA; accuracy; prevalence

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1. Introduction

Strongyloides stercoralis infection is a neglected tropical disease (NTD) affecting an estimated 640 million people worldwide [1]. The infection is transmitted through direct penetration of the skin by infective (filariform) larvae free-living in soil contaminated by human faeces. Thus, the transmission occurs in areas with inadequate sewage systems and hygienic conditions [2]. The larvae moult while migrating in the human body, and the adult female worm settles in the intestine, where it produces eggs. The newborn rhabditoid larvae hatch out of the eggs while still in the bowel and are shed with faeces. However, some of them moult into the filariform stage before leaving the body and thus can re-infect the host through rectal mucosa or perianal skin. This auto-infective cycle leads to a chronic infection, which can perpetuate through the years even in absence of re-exposure to an external infective source [2]. The infected individual can be either asymptomatic or complain of a series of unspecific symptoms, mainly involving skin and respiratory and gastrointestinal tracts [3]. Symptoms can be mild and intermittent but under some circumstances can

worsen and manifest as severe conditions. This mainly happens in immunosuppressed individuals, for whom the disseminated infection, characterized by all parasite stages migrating all over the body, represents a therapeutic challenge and is life-threatening [2]. To prevent the risk of dissemination, screening and individual diagnosis of cases followed by proper treatment of the infection, which is based on a single dose of ivermectin in case of uncomplicated disease [4], are of paramount importance, even in asymptomatic individuals. Unfortunately, there is no gold standard for the diagnosis of strongyloidiasis, and this causes an underestimation of the burden of the infection and poses infected individuals at risk of misdiagnosis [3]. Indeed, microscopy examination of stool samples has very low sensitivity for the detection of *S. stercoralis*. Although its sensitivity was demonstrated to improve with the examination of multiple samples, it still remains disappointing [5]. Baermann method and agar plate culture have better performance but are seldom done because they are time-consuming and require parasitological skills that are not widely available in non-endemic settings [6]. Polymerase chain reaction (PCR) for *S. stercoralis* demonstrated good sensitivity and specificity, though it is not yet widely available outside referral laboratories [7]. At the moment, serological tests show the best sensitivity, although cross-reactions, in particular with filarial nematodes, can cause false positive results [8,9]. However, due to the potential harm posed by the infection and the good tolerability of ivermectin, overtreatment of possible false-positive cases should be preferred to missed diagnosis and treatment.

This study was part of the Tropical Neglected Diseases Project, "Strengthening the fight against Neglected Tropical Diseases in the migrant population through the use of medical devices" that was carried out from August 2016 to July 2018. The project was led by the Italian National Institute for Health Migration and Poverty (INMP) with the collaboration of the Department of Infectious Tropical Diseases and Microbiology (DITM) of the IRCCS Sacro Cuore Don Calabria hospital, as regards the diagnostic aspects. The general objective of the project was to strengthen the fight against NTDs in migrant populations from endemic areas living in Rome through an estimate of the prevalence and an evaluation of the epidemiological characteristics of some major NTDs in order to achieve early diagnosis and care of affected migrants.

In this work, we report the results of the screening for *S. stercoralis*. Primary objective was to estimate the prevalence of strongyloidiasis in this population, based on a combination of diagnostic tests. Secondary objective was to estimate the accuracy of a novel ELISA test (Euroimmun ELISA).

2. Materials and Methods

This was a cross-sectional study, which took place from November 2017 to July 2018.

Campaigns for promotion of the screening activities were conducted in order to disseminate information about selected NTDs (in addition to strongyloidiasis, targets of the campaign were schistosomiasis and Chagas disease) and about the free access to a dedicated INMP outpatient clinic.

2.1. Participants

Migrants of any age were offered the extended screening upon spontaneous presentation to the INMP outpatient clinic. Demographic information such as data concerning migration route, personal habits, and living conditions (economic and hygienic aspects) were collected. An infectious diseases consultant sought written informed consent, provided medical visit, and asked the participants to supply faecal and blood samples for *S. stercoralis* (and other NTDs based on epidemiological risk factors) testing. Information sheets and informed consent forms were available in Italian, Spanish, English, and French. Transcultural mediators were available for illiterate people and for those speaking other languages (Arabic, for instance). Parents' or legal guardians' consent was sought for minors. All consenting consecutive participants underwent the screening and were included in the analysis. Participants received a copy of the results of the test and were treated accordingly

at the INMP clinic. Any positive test (including serology) constituted an eligibility criterion for treatment.

2.2. Test Methods

All biological samples were collected at the INMP. Aliquots were sent to the laboratory of San Camillo hospital, Rome for the full blood count. Other samples were sent to the DITM, where the following tests were carried out: microscopy examination of faeces concentrated by Ritchie's modified method, a commercial ELISA for *S. stercoralis*, an in-house immunofluorescence test (IFAT), a novel ELISA kit, and real-time PCR for *S. stercoralis*. An ELISA test for *Schistosoma mansoni* (Bordier Affinity Products SA, Crissier, Switzerland) was also done at DITM. The laboratory staff performing the serological tests were blinded towards the results of the other tests.

The ELISA commercial kit (Bordier Affinity Products SA, Crissier, Switzerland) is based on somatic antigens from larvae of *Strongyloides ratti* [10]. A previous retrospective study estimated its sensitivity and specificity at 90.8% (95% CI 85.8–95.7) and 94.0% (95% CI 91.2–96.9), respectively [9]. The test was performed as per manufacturer's instructions. A normalized optical density (OD) ratio was used to compare the results obtained in different sessions. A ratio $\geq$1 defined positive results.

IFAT was an in-house assay implemented at the DITM [11], where it is routinely used for screening and individual diagnosis. The assay is based on antigens from *S. stercoralis* filariform larvae obtained from faecal culture. Titres $\geq$ 1:20 are considered positive. The test previously demonstrated sensitivity 94.6% (95% CI 90.7–98.5) and specificity 87.4% (83.4–91.3) [9].

The ELISA performed at the DITM was a novel kit from Euroimmun. The assay is based on antigens of *Strongyloides papillosus* [12]. The test was performed per the manufacturer's instructions. Results were classified in accordance with the package leaflet: ratio <0.8 = negative; ratio $\geq$ 0.8 < 1.1 = borderline; ratio $\geq$1 = positive.

The real-time PCR is based on Verweji's method [13] and is used routinely at the DITM. Briefly, for DNA extraction, about 200 mg of faeces were suspended in 200 µL of phosphate-buffered saline containing 2% polyvinylpolypyrolidone (Sigma-Aldrich, Milan, Italy) and frozen overnight at −20 °C until the extraction. After thawing and boiling, the samples were run by an automated extractor instrument (Magnapure LC.2, Roche Diagnostics, Monza, Italy). The real-time assay was performed as described previously [13]. The amplification target was the small-subunit rRNA gene sequence for S. stercoralis. Appropriate positive and negative controls were included in all the experiments. As control for PCR inhibitors and amplification quality, the PhHV-1 control DNA was amplified with the appropriate primers/probe mix in the same reaction as S. stercoralis in multiplex PCR. The reactions, detection, and data analysis were performed with the CFX96 detection system (Bio-Rad Laboratories, Milan, Italy). In a previous retrospective study, the method demonstrated a sensitivity of 56.8% (95% CI 41.0–71.6) [14]. Specificity was considered virtually 100%.

2.3. Analysis

The sample size was based on a convenience sample constituted by all eligible participants who were enrolled during the study period. This was aimed to maximize the power and the generalizability of the study results.

Demographic and clinical data were summarized using descriptive statistics and measures of variability and precision. All parameters were reported with 95% confidence intervals (CI). For proportions, the exact Clopper–Pearson CI was computed.

Diagnostic test results were presented in contingency tables where patient's disease status was inferred based on results of each single test, the composite reference standard, and also on probabilistic models using latent class analysis (LCA) [15].

Composite reference standard (CRS) is an alternative method used for assessing test accuracy using a combination of tests and was obtained by applying the following rule:

if microscopy or PCR were positive or both IFAT and Bordier ELISA were positive, then CRS = positive; otherwise CRS = negative.

Data analysis was performed using SAS software, version 9.4 (SAS Institute, Inc., Cary, NC, USA). Statistical significance level was fixed at 0.05.

3. Results

In total, 650 participants received screening for *S. stercoralis*. Ages ranged from 8 to 73 years (median = 27, Q1 = 20, Q3 = 39), and most participants were male 463/640 (71.23%). Most participants originated from Africa (400 out of 650, 61.5%), while the remaining 38.5% came from Latin America. Overall, 318 out of 650 participants (48.92%) lived in rural areas in their country of origin; the proportion of individuals living in rural areas was higher between Africans (56.7%) than between Latin Americans (36.4%).

Symptoms were reported by 248 out of 650 (38.15%) subjects. Most frequent symptoms were pruritus and abdominal pain, reported by 206/425 (31.7%) and 180/650 (27.7%) participants, respectively. In the subgroup of participants from Africa, symptoms were reported by 226 out of 400 individuals (56.5%), while only 22 out of the 250 participants from Latin America (8.8%) had symptoms. Eosinophilia (defined as > 400 eosinophils/mcL) was detected in 102/425 (24%) individuals.

Only 635 participants were screened with real-time PCR, while the whole cohort was tested with each one of the other tests. The faecal-based tests produced the following results: 19 out of 635 (3%) participants had positive PCR, 21 out of 650 (3.2%) had positive stool microscopy. A total of 17 samples were positive to both tests. Overall, the two tests demonstrated excellent agreement (k coefficient: 0.84). A total of 18 out of the 400 participants from Africa (4.5%) had positive stool microscopy, compared to three out of 250 (1.2%) participants from Latin America. The proportion of PCR positive results was also higher for Africans (15 out of 399 individuals with the test result, 3.8%) than for Latin Americans (four out of 236, 1.7%).

The overall numbers of samples positive to Bordier ELISA, Euroimmun ELISA, and IFAT were 60/646 (9.29%), 113/648 (17.44%), and 118/646 (18.27%), respectively. The agreement between Bordier ELISA and Euroimmun, Bordier ELISA and IFAT, and Euroimmun and IFAT was moderate in all cases, k coefficients being 0.5198, 0.4106, and 0.4887, respectively. The proportion of participants with positive serological tests was similar between the two subgroups: 20.3%, 15.8%, and 9.05% participants of African origin were positive to IFAT, Euroimmun ELISA, and Bordier ELISA, respectively. The proportions of participants from Latin America with a positive result to IFAT, Euroimmun ELISA, and Bordier ELISA were 14.9%, 20%, and 9.7%, respectively.

All 23 samples with positive PCR and/or microscopy were positive to all serological methods. Additional positive samples were found by the serological tests, as displayed in Figure 1.

According to the CRS, 43 samples were classified as positive and 605 as negative. Table 1 reports the number of positive and negative Euroimmun samples against this classification.

Table 1. Proportion of positive and negative results to the Euroimmun ELISA against the composite reference standard (CRS).

	Composite Reference Standard		
Euroimmun ELISA	**Positive**	**Negative**	**Total**
Positive	40	73	113
Negative	3	532	535
Total	43	605	648

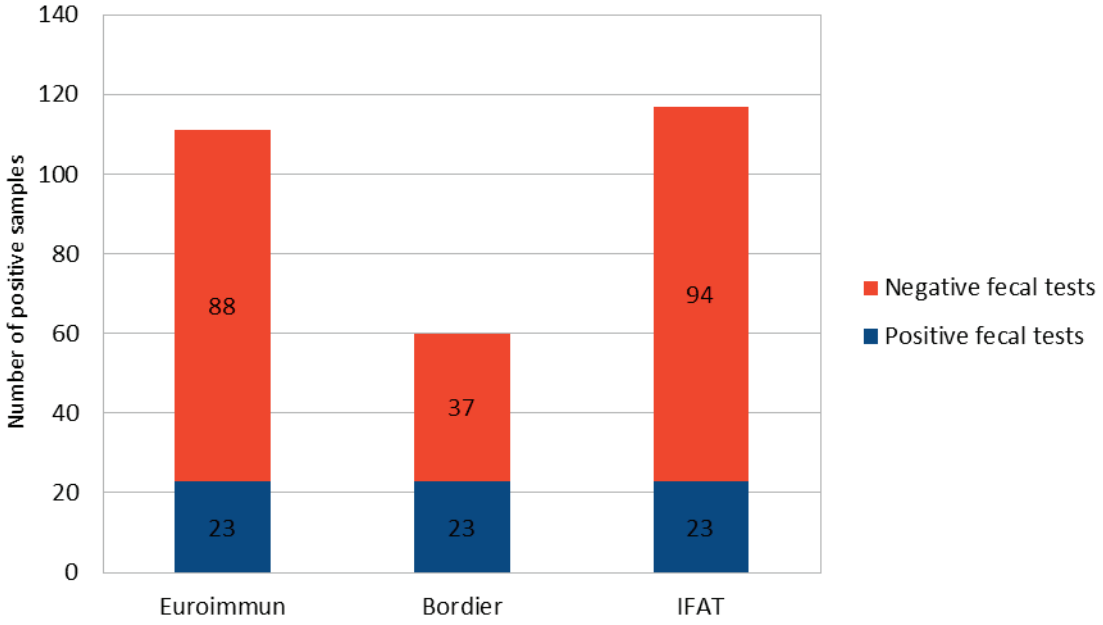

Figure 1. Positive samples to the serological tests compared to positive PCR/microscopy samples.

Sensitivity of Euroimmun ELISA was 93.2% (95%CI 80.9–98.5), specificity 87.9% (95% CI 85.1–90.4). Among the 73 false positive results (i.e., positive to Euroimmun ELISA but negative to the CRS), nine were found positive to hookworm and/or *Schistosoma* spp. Specifically, seven patients had positive ELISA, and three of them had also *S. mansoni* eggs in stools. Moreover, three patients had hookworm, one of them had also positive *S. mansoni* ELISA.

An LCA model using data from 425 participants for whom data on symptoms were available was set by adding to the results of all diagnostic tests (but Euroimmun ELISA), the clinical variables eosinophilia (p-value < 0.0001), and itching (p-value = 0.0072). Abdominal pain was excluded as it resulted statistically significant only in the univariable model (p-value = 0.0042). According to the LCA, 32 (7.5%) samples were classified as positive. Table 2 reports the number of positive and negative Euroimmun ELISA samples against this classification.

Table 2. Results of Euroimmun ELISA according to the latent class analysis (LCA) classes.

	LCA Classes		
Euroimmun ELISA	**Positive**	**Negative**	**Total**
Positive	29	48	77
Negative	3	344	347
Total	32	392	648

Based on these results, the sensitivity and the specificity of the Euroimmun ELISA were 90.6% (95%CI 80.5–100) and 87.7% (95%CI 84.5–91.0), respectively. The same helminthic co-infections (in terms of both type of helminths and number of cases) detected for the 73 false positives with the CRS were found among the 48 cases classified as false positives with the LCA.

4. Discussion

We collected data on screening for strongyloidiasis in a large cohort of immigrants from Africa (61.5%) and Latin America (38.5%). About one quarter of them presented eosinophilia, and 38% reported any symptom, mostly itching (31.7%) and abdominal pain (27.7%). About 3% of participants had a positive faecal test for *S. stercoralis* (PCR and/or

stool microscopy), while the proportion of positive serological tests ranged from 9.3% of Bordier ELISA to 18.3% of IFAT.

The Euroimmun ELISA demonstrated good accuracy, with specificity around 88% according to both CRS and LCA, and a sensitivity of 93.2% (95%CI 80.9–98.5) with the CRS, decreasing to 90.6% (95%CI 80.5–100) with the LCA.

A systematic review [16] reported a 12.2% (95%CI 9.9–15.9) seroprevalence of strongyloidiasis in migrants living in the USA, Canada, Australia, New Zealand, Israel, and Western Europe. Our findings are in line with the review, although figures vary slightly based on the serological assay considered.

It should be considered that serology tends to overestimate the prevalence of strongyloidiasis based on the lower specificity compared to faecal-based tests caused by possible cross-reactions [9]. Here, we report a few co-helminthic infections that could be the cause of false positive results but, for instance, filarial nematodes were not thoroughly investigated. Although lower specificity might be acceptable in specific contexts (e.g., screen and treat strategies), a classification based on a combination of diagnostic tests can be more appropriate in others. As an example, surveys of prevalence in endemic areas can benefit from the addition of a more specific test, as co-infections with helminths that can cause cross-reactions are of higher concern in that setting. Here, we adopted two different approaches to the classification of positive/negative cases, which are CRS and LCA. With these methods, we classified as positive 6.6% and 7.5% cases, respectively. These figures, which are between the 3% found with faecal tests and a maximum of 18% with IFAT serology, can presumably give a better idea of the real prevalence of strongyloidiasis found in our cohort.

Eosinophilia and itching were included in the LCA on the basis of significant association with *S. stercoralis* infection in a multivariate analysis. Abdominal pain was significantly associated with the infection only in the univariate model, and other symptoms (for instance respiratory symptoms, weakness) did not show any association. Eosinophilia has repeatedly been reported as a frequent feature of strongyloidiasis, while clinical presentation is more debated, as symptoms are often intermittent and aspecific [17,18]. A systematic review of studies carried out in *Strongyloides* endemic areas [19] showed association with urticaria, while itching was frequent but the association was uncertain (though we might debate that itching is presumably associated with urticaria).

An unexpected result of our analysis is the excellent agreement between stool microscopy and PCR. Indeed, stool microscopy is usually considered to have a sensitivity exceedingly low compared to PCR [8]. The results of microscopy here (3.2% positive participants) are in line with a previous study reporting data on screening of 462 asylum seekers in Northern Italy [20], where 3.3% positive individuals were found with stool microscopy (with modified Ritchie's concentration method). In other studies, the screening of populations at risk resulted in a higher proportion of individuals positive to *S. stercoralis* detected by PCR than other parasitological methods [6,21,22].

Here, it should be considered that laboratory staff performing microscopy was not blinded to the results of PCR, thus this might have caused a more intense examination of stool samples when PCR was positive. Conversely, agreement between the pair of serological assays was found good in all cases. In literature, we could find only a few conference proceedings reporting data on accuracy of Euroimmun ELISA, which was deemed good in comparison with other ELISAs [12,23]. Hence, to our knowledge, this is the first work reporting full data on the evaluation of this assay, which demonstrated good performance for the screening of individuals at risk of strongyloidiasis.

Finally, another limitation of the study is that prevalence of the infection was assessed in a group of migrants who spontaneously presented to the clinic. Thus, they might have been motivated by presence of symptoms or other health concerns, reducing the presence of asymptomatic infections in the cohort.

5. Conclusions

In a cohort of 650 individuals from Africa (61.5%) and Latin America (38.5%), screening with different diagnostic methods for *S. stercoralis* showed a prevalence of strongyloidiasis of about 7%. As expected, a higher proportion of positive results was found with serological tests than with faecal-based tests. Unexpectedly, Ritchie's concentration stool microscopy showed excellent agreement with PCR for *S. stercoralis*. The accuracy of a novel ELISA (Euroimmun) kit was found good, indicating that the assay would be useful for screening activities.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee of the Italian National Istitute of Health (Istituto Superiore di Sanità) on 20 September 2016 (protocol code PRE-712/16).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The study database will be available in Mendeley Data upon acceptance for publication.

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5.2 Current and future research on schistosomiasis diagnostics

In the population of African patients described in Chapter 4, diagnostic difficulties emerged with regard to schistosomiasis, which nevertheless represents a very high burden with thousands of cases estimated in Italy in the population of African origin, and largely undiagnosed, as shown by our work and previous works. (3,7).

The first work we propose to do is a rigorous evaluation of the diagnostic accuracy of the tests used in our longitudinal study, both with the Composite Reference Standard (CRS) method already described for estimating the prevalence of infection, and with the more sophisticated Bayesian Latent Class Analysis. Moreover, since among the serological methods, in a previous study, the rapid diagnostic test (RDT) on serum proved to be the most sensitive, so much so that it was considered as a possible test to be used alone for screening, it will be interesting to prospectively evaluate, by our and/or other research groups, the accuracy of a recently developed prototype for the use of the same test on blood obtained by finger-prick, which would have an obvious advantage in terms of practicality, as it could theoretically be carried out at the first level of contact between the migrant or asylum seeker and the health system.

A third line of research concerns the evaluation of the accuracy of a new molecular test to be used on serum samples, developed at DITM (qPCR) and already carried out very recently on specimens from the same subjects included in our study (chapter 4). The test is species specific (i.e. it is able to distinguish between *S. mansoni* and *S. haematobium* infection). From preliminary results on the samples tested, the test proved to be significantly more sensitive than both qPCR on faeces for *S. mansoni* and qPCR on urine for *S. haematobium* (results not shown as the analysis is still underway). This test would have the great advantage of distinguishing between current and previous infections and could also be used as a test to monitor the effectiveness of treatment.

CONCLUSIONS

Dealing with the health of migrants, victims of trafficking, unaccompanied minors, asylum seekers and international protection and, therefore, vulnerable and 'neglected' people cannot disregard their socio-cultural, geopolitical and economic context, the type and duration of the migratory journey, the living conditions in the countries of origin and arrival.

If this is true in general, it is even more so when the 'neglected' people are affected by diseases that afflict the poorest populations, increase the poverty and have a low priority on the political and scientific agenda, resulting in difficult access to diagnosis and treatment.

Taking care of migrants by shedding scientific light on health issues, on the one hand puts the spotlight on health aspects that require specific interventions (such as NTDs) or help to dispel false, sometimes politically determined myths, such as that of the migrant as an infectious disease spreader, and on the other hand restores dignity to people and scientific dignity to diseases.

The complexity of caring for migrants is, therefore, the result of an intriguing and intriguing relationship of ethics, science, solidarity, rights, politics, health determinants, where everything intersects and blurs indistinctly, thus becoming a challenge for global health.

I would like to conclude this thesis on NTDs and these years of my doctorate with the words of Carlo Urbani, doctor of neglected diseases, during his speech at the Nobel Prize ceremony in November 1999:

Health and dignity are indistinguishable in the human being; our commitment is to remain close to the victims, to protect their rights, far from all frontiers of discrimination and division...And then to tell, to shout about the deprivations of the dispossessed, the remoteness of the excluded... we who have the privilege of doing a job that makes us look people in the eye, makes us touch people, from that position of proximity to the violated individuals, we will continue to call politicians to their duty, shouting the suffering of our patients at the microphones, for action at the roots of the evils we observe are convinced that even if words do not save lives, silence kills them!

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[1] Most references are included in the articles and are not repeated here.

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