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Abstract

Background: Screenings for infectious diseases in asymptomatic immigrants.

Aims: We describe the frequency of infections in a cohort of newly arrived asymptomatic immigrants in Southern Italy.

Methods: We studied a cohort of 238 Sub-Saharan African and Asian men attending a Reception Centre (CARA) in Foggia, between January and December 2015. The tuberculin skin test for diagnosis of Latent Tuberculosis Infection (LTBI) and serology/virology testing for HBV, HCV, HIV were performed on the subjects.

Results: Two hundred and five subjects agreed to be tested only for serological/virological markers, while 82 individuals agreed to be tested for LTBI; only 49 subjects performed both tests. Among subjects tested for virological markers, 23/205 (11.2%) were HBsAg positive; 12/23 (52.2%) individuals had chronic active hepatitis; 77/205 (37.6%) individuals had only anti-HBc positivity. HCV infection was present in 8/205 (3.9%) individuals, and chronic HCV hepatitis, was only diagnosed in two subjects. Only 2/205 (1.0%) subjects presented anti-HIV and HIV-RNA positivity. A LTBI was found in 29.6% of TB tested subjects.
Conclusions: Asymptomatic immigrants are at increased risk for some infections, mainly HBV and tuberculosis.

Keywords: epidemiology, infectious diseases, immigrants, newly arrived, Italy

https://doi.org/10.26719/emhj.18.035

Received: 15/02/17; accepted: 11/10/17

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Introduction

The last 20 years has seen considerable migration from low- and middle-income countries to high-income nations, primarily the United States of America and western Europe. On 1 January 2016, the number of people living in an European Union (EU) member state who were citizens of non-member countries was 20.7 million. In Italy this represented about 4 million people or 6.7% of the population(1). This remarkable increase in people, whose living conditions are often considerably disadvantaged, has sometimes led to problems not only of a socio-economic and security nature, but also of sanitation and health. In fact, while most tropical diseases in Italy are absent or sporadically appear (2,3), it was observed that the prevalence/incidence of other pathologies such as HBV/HCV/HIV/TB have changed their epidemiology over the years in Italy, in relation to the immigration phenomenon. Some infections have been directly imported, both in latent and active forms. Others have been heavily contracted by immigrants, due to living conditions/habits with an increase in some infectious diseases (HIV (3), TB (4), viral hepatitis (5,6) and, sometimes, their co-infections (6).

Southern Italy has been, and still is, a major destination for illegal immigration (African, Middle Eastern and Asian) from the North African coast (7). On arrival, the immigrants are hosted in reception centres (CARA), which are distributed in various parts of Italy. Most are young and healthy individuals, but they are often considered a source of certain infectious diseases such as Ebola, SARS etc., occasionally resulting in unjustified prejudice, because of their geographic origin, ethnicity, health conditions at the departure point, and the migratory route (8–10).
Therefore, the identification and treatment of any imported asymptomatic infections could reduce their incidence/prevalence and modify their outcome. This can have a significant clinical and psychological impact both for the individual concerned and for public health (10).

The health service for immigrants in Italy, particularly for clandestines, is not adequate and most assistance is currently provided by religious or lay volunteer groups. Only recently have hospitals and local health services initiated the creation of out-patient clinics for immigrants, including soliciting the help of cultural workers and interpreters (10). In such a challenging scenario, the team of volunteer doctors in this study have been screening immigrants hosted in the CARA of Foggia (Apulia, Southern Italy) for infectious diseases, for several years. The aim of this research, conducted in the year 2015, was to determine the possible presence of HIV/HBV/HCV/TB infections in a cohort of asymptomatic immigrants who were temporarily guests at the CARA of Foggia, and to measure the burden of those latent or active infections, potentially harmful for the individuals' health and transmissible to the community.

**Methods**

Between January and December 2015, we screened 238 asymptomatic immigrants for HIV/HBV/HCV/TB. Before screening, all guests at the CARA (728 subjects) were informed about the purpose of the study and invited to participate. Subsequent recruitment has been on a voluntary basis; the recruitment adhesion of minors was mediated by tutors. The study was reviewed and approved by the general manager and the medical director of the CARA, and a written informed consent, provided in four languages (English, French, Arabic and Italian) was obtained from each study subject. All study procedures were in agreement with the Helsinki Declaration (1975, amended in 2008).

At the time of enrolment all participants were interviewed using a questionnaire to obtain demographic and clinical information. None of the screened patients reported previous exposure to infectious diseases, neither vaccination for hepatitis B, nor vaccination or anti-tuberculosis prophylaxis. All enlisted subjects went through complete clinical tests and, if necessary, we proceeded with further diagnostic tests and treatment. In addition, we implemented a strategy to prevent spread to other immigrants and indigenous populations, who lived in close contact with infected persons. Diagnoses of infections were made using standard commercial tests. The health examination performed for all asymptomatic immigrants was based on systematic screening that included serological and virological examination for selected infections: HIV, HBV, HCV virus, and the search for possible latent tuberculosis infection (LTBI) using the tuberculin skin test (TST).

**Statistical analysis**
Categorical data are presented as absolute numbers and proportions. Continuous variables were summarized as mean and standard deviation (SD), and categorical variables as absolute and relative frequencies. Differences in the mean values for continuous variables (age, HBV genotypes) were evaluated by the Student’s t-test for independent samples. The Chi-square test was applied to compare categorical variables (ethnicities, HIV/HCV antibodies, HBV markers and TST positivity). P < 0.05 was considered statistically significant.

Results
Demographic characteristics

One hundred and thirty-two of the 238 enrolled study subjects (55.5%) came from Sub-Saharan African (SSA) countries, (54.2% from East Africa, 35.9% from West Africa, 10.8% from Central Africa), 106 (44.5%) from Asia, mainly from the Indian subcontinent and Pakistan. The mean age was 25.1 ± 5.7 years (13–40 years); all of them were men, since the population of the CARA was exclusively male. Subjects were in Italy for a mean period of 36 days (7–118 days) (Table 1). Among the study population, 205/238 immigrants (86.1%, 111 Africans, 94 Asians) agreed to be tested only for serological/virological markers (HBsAg/anti-HBc, anti-HCV, anti-HIV) and 82 individuals agreed to be tested for TB (TST). Only 49 subjects agreed to receive both tests (Table 2).

HBV infection

Among tested subjects, 23/205 (11.2%) were HBsAg positive: 17/23 (73.9%) Africans and 6/23 (26.1%) Asians (P = 0.03). Sixteen patients were anti-HBe positive while seven (two of which were Asians) presented HBV-wildtype (HBsAg/HBeAg positive). Chronic active HBV (CHB) infection, with HBV-DNA detectable by real time PCR, was present by 12/23 (10 Africans and two Asians, P = 0.03; 52.2%) HBsAg positive individuals (mean level 1,374,231 copies/mL, range 74,651–13,875,247). Nine CHB patients presented e-minus mutant virus and three had HBV-wildtype virus. Genotype distribution, among all CHB/HBV-DNA positive patients, was: 5/12 patients had genotype E (51.7%), 3/12 genotype A (25.0%), 2/12 genotype D (16.7%), 1/12 genotype B (8.3%), and 1/12 genotype C (8.3%). Genotypes E, A and D were associated with the African subgroup, while genotypes C and B were associated with the Asian subgroup.

A significant statistical difference was observed between genotype E and the other genotypes (P = 0.02), while the difference in prevalence between the genotypes A, B, C and D (P = 0.08) was modest. Seventy-seven individuals (37.6%) had anti-HBc positivity (OBI), a bio-marker of previous HBV infection. The prevalence among sub-Saharan Africans was 66.2% (51/77 patients), compared to 33.8% (26/77 patients) among Asians (P = 0.03). All subjects denied having previous HBV vaccinations in their country of origin. Five out of 77 subjects (with slightly hypertransaminasemia) had HBV-BNA positivity with a low viral load (mean level 1,275
copies/mL, range 471–5743); genotyping was not performed.

**HCV infection**

HCV infection was present in 8/205 individuals (3.9%): 3/8 (37.5%) were Africans and 5/8 (62.5%) were Asians (P = 0.02). Chronic HCV-infection, with the presence of HCV-RNA detectable by real time PCR, was diagnosed only in three Asian patients; HCV genotyping was performed in these individuals: two presented genotype 1a and one presented genotype 3.

**HIV infection**

Only 2/205 (1.0%) individuals presented anti-HIV antibodies, and, subsequently, we were able to detect HIV-RNA. One subject was African and the other was Asian. The HIV-positive immigrants were not aware of their serologic status before their arrival or, at least, they did not acknowledge a sero-positivity for HIV. Neither of the two patients showed an AIDS-defining disease or other clinical symptoms at the time of screening; only one patient developed pulmonary active tuberculosis during the first month of follow-up.

**Viral co-infections**

Five patients (three Africans and two Asians) showed HBV-HCV co-infection: in four cases HBV infection was prevalent, while in one case HCV virus infection prevailed. HIV-HBV-HCV co-infection was present only in the HIV-positive African subject.

**Latent tuberculosis infection**

Only 82/238 (34.5%) individuals of the study population agreed to undergo tuberculin test (56/82-76.7% Africans and 24/82-29.3% Asians) (P = 0.02). Among patients tested with TST, 11 subjects (eight Africans and three Asians) did not return for the control. TST was positive (>10 mm) in 21 (29.6%) of the remaining 71 individuals. Prevalence of LTBI was significantly more frequent among Africans (71.4%; 15/21) than among Asians (28.6%; 6/21) (P = 0.02). One of the TST-positive subjects was also HIV-positive. None of the patients who were TST positive presented radiological and microbiological signs of pulmonary active tuberculosis. All data are described in Table 2.

**Discussion**

The ever-increasing presence of immigrants fosters feelings of fear in the native Italian population; fear that they may introduce new and unfamiliar diseases, such as SARS, MERS, Ebola, Dengue, etc., or pathologies which are no longer present or have almost been eradicated from the country (11). Many of these infections may be asymptomatic for long
periods and manifest themselves later in life as active diseases. This means that the incidence of certain illness may increase in host countries despite autochthonous cases declining (12).

HBV-infection represents a prevalent infectious disease in immigrants, particularly in people coming from SSA areas, with a high rate of infection ( >8%). This figure is most likely caused by the lack of or incomplete prophylactic vaccination in the country of origin, and risky sexual behaviour (13–15). In our study we evaluated the prevalence, the typology of HBV-infection and the degree of disease, based on genotype. Our findings (HBsAg positive rate: 11.2%) reflect the current prevalent migratory flow to our geographic area, which is mostly represented by people coming from SSA. In contrast, HBV infection is rarely observed in Asian immigrants (16–18). This data, showing the differences in infection rates due to ethnicities, highlights the epidemiological pattern of the prevalence of HBV based on the country of origin (13,19–21). Among these subjects, more than half had CHB, indication of a previous infection, with a clear majority of subjects from SSA (10/12 patients). The prevalence of HBV infection was similar in African children (<16 years) and adults. This result leads us to postulate that the infection may occur at an early age (by vertical transmission or in childhood), in contrast with what has been observed in Western countries (17).

Most cases were infected by genotype E, which is almost exclusively diffused in SSA (18,21). Other HBV genotypes were also found, like D-B-C-A, thus reflecting different areas of origin (22–24). This redistribution of HBV genotypes represents an important change in the epidemiology of infection. In Italy, this increases the number of subjects infected with a “different” hepatitis, despite the risk of reinfection with a virus of a different genotype for the Italian population being low, because HBV vaccination protects from all HBV genotypes. A high proportion of patients (37.56%) had only anti-HBc (OBI), a marker that can be indicative of either natural or artificial immunization or occult active hepatitis. This clinical situation seems to be quite frequent among Sub-Saharan individuals (18,24).

Careful evaluation of OBI in the immigrant population is important because: OBI can be transmitted through transfusion, organ transplantation, or haemodialysis; OBI may reactivate and cause acute hepatitis in immune-compromised patients; and OBI may contribute to the progression of hepatic fibrosis in patients with other chronic liver diseases and constitute a risk factor for hepatocellular carcinoma (25–27). Therefore, it is evident that immigrant subjects with OBI may, if not carefully controlled, represent a risk for themselves and for the indigenous population. Currently there is no agreement on how to classify and manage individuals with OBI. Some authors suggest testing for HBV–DNA when alanine aminotransferase (ALT) levels are elevated (28), while others recommend the test only if there are other risk factors for liver diseases, even with normal ALT levels (28,29). We decided to check for HBV-DNA only in five subjects who had high levels of serum ALT.
The prevalence of HCV-infection in Europe reliably indicates that about 1% of the total population is affected, albeit with regional differences (16). However, from research carried out in different countries it emerged that immigrants seem to have a very high risk of contracting HCV-infection after their arrival in host countries (30). In Italy, the prevalence of HCV among immigrants is variable due to both the period and the area of research (different ethnicities), but generally it is higher than that of the local population. In fact, it ranged from 2.7% in 2008 in Verona (31) to up to 15.2% in 2015 in Sicily (32), with a national percentage comprised between 4 and 5.6%. In this study on newly arrived immigrants, the rate of prevalence was superimposable (3.9%); the patients were mainly Asians, especially Pakistani (5.3%), while among Africans the rate was lower (2.7%).

Such differences, as deduced from the reported risk factors, seem to be related to intravenous drug addiction, more common among the screened Asians than the Africans (9). Another risk factor was the high percentage of sexually transmitted infections (33), since all the screened HCV positive Africans were infected via this route. An additional risk factor could have been infection via blood transfusion, blood derivative products, or following invasive procedures (surgery, endoscopic tests, etc.) performed with inadequately sterilized instruments (34,35). These events are not infrequent in some Asian countries, where although public healthcare systems are accessible, they are not always at a level to prevent nosocomial infections. In contrast, in many parts of Africa, mainly in SSA, due to an almost total absence of a healthcare system, the possibility of carrying out invasive procedures or blood transfusions is very small. Consequently, although such a situation impedes the provision of adequate healthcare to people, it certainly helps comparatively lower rates of diffusion of hepatitis C virus (11,34,35).

Screening for HIV is systematically recommended in those individuals coming from countries and communities where HIV prevalence is ≥ 0.1%, such as immigrants coming from SSA and Asian countries. In fact, in these populations the risk of HIV-infection is greater than in the native population and in particular, the incidence of new HIV diagnoses in Italy is estimated to be eight times higher in immigrants than in Italians (21). However, in our screened population, the overall prevalence of HIV-infection was 1.0%, which is quite low considering that the rate of HIV-infections in the majority of native countries of the immigrants is much higher than in Western countries, including Italy. This data confirms, after many years, previous findings from our research group that highlighted that newly arrived immigrants (< 2months) had a 1.5% prevalence of HIV-infections (36).

This low rate could possibly be explained by the statistical bias known as the “healthy migrant effect,” for which immigrants are “positively selected” from among their original population as individuals more apt to embark on such a strenuous migratory project. These migrant health
advantages, however, tend to vanish over time due to high-risk behaviours. Regarding HIV-infection, the preponderance of young sexually active males is already a risk factor, enhanced by contacts between parties belonging to the same ethnic group. Therefore, the low prevalence of HIV-infection in our cohort of recently arrived individuals, despite the high incidence of infection in immigrants’ resident in the country reported in previous studies, seems to suggest that HIV-infection is more often acquired during permanence in the host country rather than imported from the country of origin (37–39).

Active tuberculosis (TB) is an increasing problem among immigrants living in Western countries (40). It may be the clinical expression of a new infection acquired in the host country or more often the reactivation of a latent form (LTBI) brought from their country of origin (40,41). Also in Italy it has been shown that, in recent years, > 50% of new cases of TB affect immigrant subjects (41,42). LTBI represents a state of equilibrium in which the host can control the infection, but cannot completely eradicate the bacteria. This is related to a persistent immune response to stimulation by Mycobacterium tuberculosis antigens; therefore, infected subjects can be entirely asymptomatic. The greatest danger is in reactivation (active TB after remote infection) cases, and the subsequent silent spread to close contacts. Therefore, patients with LTBI are the largest reservoir for potential transmission.

A high prevalence of LTBI with rates of 52–72% and elevated risk for TB reactivation, with rates of 7.8%, was observed in immigrants within the first two to five years after arrival (43,44), making tuberculosis the most relevant infectious disease currently. This is predominantly among immigrants from highly endemic areas such as SSA and the Indian subcontinent. The peculiar aspect of this study is the population screened, consisting of recent immigrants residing in Italy for no longer than three months. Only a minority of screened immigrant people (82/238) volunteered for the TST, and 11 of them (13.4%) did not turn up to be checked, perhaps for fear of expulsion. The prevalence of positivity for TST was of 29.6%, a rate lower than what was observed in other studies (43,44). This low rate of positivity could be due to errors in the administration and reading of TST as this technique was performed “on the field” and not in a hospital setting, and subjectivity is one of TST’s main limitations, even though it was performed by trained personnel. The presence of immunosuppression could also influence TST results, even if only a few studies are available (44). Our results were not influenced by HIV-related immunosuppression because only one patient was HIV positive with a low viral load; but other causes of immunodeficiency, such as malnutrition and fatigue, cannot be excluded for the most recently arrived subjects, due to the hardships of their migratory journey.

**Conclusions**

Most immigrants are healthy people, but can also constitute a population at risk because they might be asymptomatic carriers of infections that might be activated at a later time. It is important to determine the presence of pathologies for both the immigrants and the potential
public health implications. Therefore, every country that welcomes immigrants, must implement affordable and cost-effective screening protocols. These programmes should be characterized by the principles of equality and respect for the immigrant subject, and be aimed at both the health of the individual and that of the host community. Such programmes could follow the example of Italy, where many public health facilities have voluntarily opened outpatient clinics dedicated to immigrants.

Acknowledgements

The authors are grateful to Paola Silvino and Pasquale Di Molfetta (CARA, Borgo Mezzanone, Foggia, Italy) for their kind collaboration.

Funding: None.

Competing interests: None declared.

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