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Screening for hepatitis B virus infection among refugees diagnosed with latent tuberculosis in an Italian community

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Abstract

Background. *Refugees are a growing population in the EU-27 area with specific health needs that are to be addressed in the most rapid and effective way at their arrival in the host country. Screening for Hepatitis B Virus infection is offered to specific categories and it could be useful and effective to extend its indications. The aim of this study was to define the epidemiological profile regarding Hepatitis B Virus infection in refugees hosted in the Asylum Seekers Centers of Verona (Italy), diagnosed with latent tuberculosis infection and eligible for chemoprophylaxis.*

Methods. *We conducted a retrospective study in 715 refugees diagnosed with latent tuberculosis infection from January 1st, 2015 to December 31st, 2017. Screening for Hepatitis B Virus infection was offered to latent tuberculosis infection patients who were due to commence treatment. Subjects were tested for Hepatitis B surface Antigen and Hepatitis B core antigen total antibodies. None of the screened patients reported previous vaccination for hepatitis B.*

Results. *Among the 715 refugees diagnosed with latent tuberculosis infection, 593 were eligible for treatment for latent tuberculosis infection. Of these, 211 (35.6%) accepted to be screened for Hepatitis B Virus infection. One hundred and ninety-five of the 211 (92.4%) came from African countries, and 16 (7.6%) from Asia; the majority (80.9%) were males. Median age was 23 years (95% CI 22-24). Of the 211, 58 individuals (27.5%) were Hepatitis B surface Antigen and Hepatitis B core antigen total antibodies positive; 74 (35.1%) were Hepatitis B surface Antigen negative and Hepatitis B core antigen total antibodies positive; and 79 (37.4%) were Hepatitis B surface Antigen and Hepatitis B core antigen total antibodies negative. Male gender and African origin were associated with a lower probability of being Hepatitis B surface Antigen- and Hepatitis B core antigen total antibodies-negative.*

Conclusions. *Screening for Hepatitis B Virus is of paramount importance not only for the control and prevention of infection, but also in terms of long-term healthcare issues. Making screening more systematic can have an important impact on public health, while always considering cost-effectiveness and promotion of awareness among ethnic groups in order to gain their compliance to treatment/vaccination.*

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Introduction

Migration is a phenomenon that has always occurred in Italy, first as outward migration of its resident population (especially in the 19th and 20th centuries), and now mainly as inward migration. As a European country, Italy welcomes important flows of individuals leaving African, Asian and Eastern European countries for economic, social and political reasons. In 2020, 34,134 migrants arrived in Italy, and 4,623 of them were unaccompanied minors (1). By December 31st, 2020, the total number of migrants received on the Italian territory was 79,938. Among the declared countries of origin, the most represented were African countries (Tunisia 38%, Ivory Coast 6%, Algeria 4%, Egypt 4%, Sudan 3%, and Morocco 3%), followed by countries of the Middle-East and Indian sub-continent (Bangladesh 12%, Pakistan 4%, Afghanistan 3%, and Iran 3%) (1).

The need to seek international protection is one of the reasons why individuals leave their country of origin. Asylum is a form of international protection offered by a state on its territory. It is granted to people who are persecuted for reasons of race, religion, nationality, membership of a particular social group or political opinions, and do not receive protection in their state of citizenship and/or residence. Recently, the United Nations Human Rights Office called upon governments to consider climate change as another reason why refugees should be granted asylum (2). Between 2008 and 2012, there has been a gradual increase in the number of asylum applications in the current 27 Member States of the European Union (EU-27), reaching 1.2 million applications in 2016 (3). There were 10,972 asylum applications submitted to Italy from 1st January to June 12th 2020. With regard to the countries of origin of applicants, the most represented was Pakistan with 18% of applications, followed by Nigeria (10%). Seventy-six percent of applicants in the reported period were males, 24% females. Most of them (62%) were between 18 and 34 years old, 13% were children aged 0-13 and 3% were aged 14-17 (4). Under the Italian law, asylum seekers are hosted in Asylum Seekers Centers.

The search of tuberculosis (TB) disease is part of the preliminary medical assessment of all migrants during the reception process. In accordance with the 'Public health guidance on screening and vaccination for infectious diseases in newly arrived migrants within the EU/EEA', issued by the European Center for Disease Prevention and Control (ECDC) in 2018 (5), Italy offers chest X-rays to symptomatic subjects (cough lasting for more than two weeks), and a tuberculin skin test (TST) (alternatively interferon-gamma release assay, IGRA, in particular in those previously vaccinated) to all asymptomatic subjects coming from countries with high incidence of TB disease (>100/100,000 inhabitants) who are expecting to stay for at least six months, and link to care and treatment when indicated (6). Migrants usually represent the main reservoir of TB disease in developed countries with low prevalence rate of infection (7).

Hepatitis B virus (HBV) infection is worldwide spread with about 240 million people infected (defined as Hepatitis B surface Antigen positive, or HBsAg+) and a different geographical distribution. Hepatitis B prevalence is highest in sub-Saharan Africa and East Asia, where between 5-10% of the adult population is chronically infected. In the Middle East and the Indian subcontinent, an estimated 2-5% of the general population is chronically infected. In Western Europe and North America, less than 1% of the population is chronically infected. Italy is a country with a low level of HBV infection prevalence, characterized by a percentage of chronic carriers of about 1.5% (8). Italian guidelines 'Sanitary controls and pathways for newly arrived migrants hosted in receptions centers' advise to offer HBV

screening to migrants during the second phase of the reception, specifically to individuals from countries with HBsAg prevalence >2%, and - regardless of the country of origin - to those who meet at least one of the following criteria: concomitant HIV infection, previous blood transfusion, intravenous drug addiction, multiple sexual partners, victim of sexual abuse, close contact with HBsAg-positive relatives, ongoing immunosuppressive treatment, and pregnancy (6). Currently, concomitant TB infection is not considered an indication to offer HBV screening, even though areas of high HBV prevalence are similar to the global TB epidemiological "hotspots" (sub-Saharan Africa and South Asia) (8). On the other hand, the most accurate assessment of the prevalence of HBV infection among refugees is considered increasingly important, and also necessary to avoid a huge unknown reservoir of untreated hepatitis B in Europe resulting in an increased burden of cirrhosis and hepatocellular carcinoma diagnosed in late stages. In addition, the rapid diagnosis of multiple concurrent infections is of particular importance for the health of migrants, whose general state of health is often already compromised, for a more targeted and effective treatment. This is particularly important in the case of *Mycobacterium tuberculosis* and hepatitis B virus co-infection, as anti-tubercular therapy is associated with adverse events, including fatal ones, which occur with greater frequency and severity in patients whose liver is already damaged.

This study is part of a wider project aimed at assessing the prevalence of latent tuberculosis infection (LTBI) in refugees hosted in the Asylum Seekers Centers of Verona (Italy) during an observation period of 36 months. The aim of the present study was to define the epidemiological profile as regard to HBV infection in refugees diagnosed with LTBI and eligible for chemoprophylaxis, to provide with data to support decisions regarding screening and vaccination policies in the migrant population.

Materials and methods

A retrospective study was conducted in the migrant population hosted in the Asylum Seekers Centers of the province of Verona (North-Eastern Italy) from January 1st, 2015 to December 31st, 2017. Refugees, asylum seekers, and economic migrants who arrive in Italy mainly through the flows in the Mediterranean Sea are filed at the point of arrival in accordance with Italian laws and EC agreements and then sent to various regional centers according to availability. Asylum seekers sent to the Centers of Verona were referred to the Migrants' Service within the Territorial Department of Prevention in Verona. In the context of the medical examination, particular attention is paid to clinical, family and social history, as well as to the active search for signs and/or symptoms suggestive of specific morbid conditions - in particular TB infection, malaria, sexually-transmitted diseases, parasitic infections, anemias, diabetes - in order to ensure timely access to treatment. The results of screening for conditions other than TB and hepatitis B are not presented in this study. The average timeframe between the arrival in Italy and the screening is 7 days.

The screening process for LTBI has been described in details in another study from our group (9). In brief, TST was offered to migrants during the first examination and a diameter of induration ≥15 mm was considered to be positive; a diameter between 5 and 14 mm was considered as indeterminate and a confirmatory IGRA was performed. LTBI was defined as an asymptomatic patient with a positive result of the TST and without radiographic evidence of active TB disease. None of the screened patients reported previous vaccination for hepatitis

B, nor BCG-vaccination. Patients diagnosed with LTBI were offered standard therapy (Rifampin, Isoniazid), if eligible (10).

Screening for HBV infection was offered to LTBI patients who were due to commence the treatment regimen. Subjects were tested for HBsAg and Hepatitis B core antigen total antibodies (HBcAb). HBV infection was defined by positive HBsAg and HBcAb; immune status was defined by positive HBcAb and negative HBsAg; if both HBsAg and HBcAb were negative, given the fact that none reported previous vaccination for hepatitis B, the subject was considered vulnerable to HBV infection.

Data were analyzed using Stata software, version 16 (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC). Descriptive statistics for continuous variables included the number of migrants, median and 95% CI. For categorical variables, frequencies and percentages were presented. We compared the differences in characteristics between migrants according to the screening results. We used the Chi-square test, or the Fisher's exact test when appropriate, for categorical variables, and Kruskal-Wallis test for comparison of more than two groups. Logistic regression analysis was performed to ascertain the effect of gender, region of origin (Africa vs. Asia), and age on susceptibility to HBV infection. Age was converted from a continuous to a categorical variable of <24 and ≥24 years.

Results

The number of asylum seekers hosted in the reception centers of the province of Verona in the 36 months considered was 2,486. The origin of the subjects was distributed as follows: 2,030 (81.6%) from the African continent (respectively, 80.9% from sub-Saharan Africa, and 0.7% from North Africa), 431 (17.3%) from Asia (Middle East and Indian subcontinent), and 25 (1.1%) from Eastern Europe. The TST was taken by 97.3% (2418/2486) of the refugee population. As a result of the general TB screening, LTBI was diagnosed in 715 individuals, with a prevalence of 28.8% (95% CI 26.98-30.54). Refugees diagnosed with LTBI included more males (93.4%), subjects older than 24 years old (54.0%), and people of African origin (86.6%) (P<0.05) (9).

Among the 715 diagnosed with LTBI, 593 patients were eligible for treatment for latent TB infection. Of these, 211 (35.6%) accepted to be screened for HBV infection. Figure 1 summarizes the screening process. One hundred and ninety-five of the 211 (92.4%) came from African countries, and 16 (7.6%) from Asia. The majority (80.9%) were males. Median age was 23 years (95% CI 22-24). Table 1 reports the descriptive data of the population undergoing HBV screening and the distribution of screening results. Also, the main characteristics of the individuals according to screening outcomes are compared. Of the 211, 58 individuals (27.5%) were HBsAg and HBcAb positive; 74 (35.1%) were HBsAg negative and HBcAb positive; 79 (37.4%) were HBsAg and HBcAb negative. The logistic regression model indicated that male gender (OR 0.39, 95% CI 0.19-0.79) and African origin (OR 0.33, 95% CI 0.11-1.02) were associated with a lower probability of being HBsAg- and HBcAb-negative, whereas age (OR 0.72, 95% CI 0.40 - 1.29) was not an associated factor.

Discussion

Infectious diseases are an essential aspect of analysis when studying the effects of migration flows of peoples. Migrants, especially coming from African regions, carry higher prevalence rates of TB infection and HBV infection than European natives (11). In Italy, 4,400 cases of TB infection were notified in 2017, with an estimated

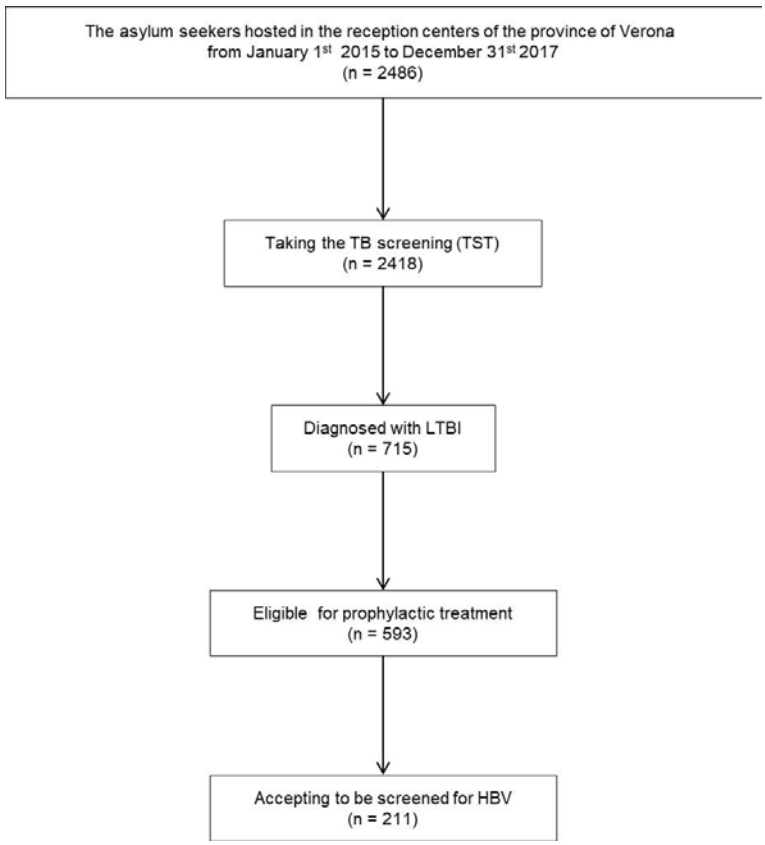

Figure 1 - Flow chart of the screening process.

rate of 7.4 per 100,000, slightly higher than in 2015 (6.2) (12). With regard to migrants, data from the Italian Ministry of Health indicate that, since 2009, the percentage of cases reported to foreign-born citizens has exceeded that of those born in Italy, with a peak of 56% in 2012 (13). The growing number of cases can be explained by the demographic increase (13). Nonetheless, it remains undeniable that migrants are particularly vulnerable to the development of active tuberculosis, due to the higher prevalence of latent infection in individuals coming from high endemic areas, but above all due to the conditions of vulnerability and precariousness, as well as the objective difficulties in accessing prevention, diagnosis and treatment services (12). The tuberculosis screening uptake, defined as the percentage of persons who agreed to be screened after being offered screening, was satisfactory in our group, thanks to the presence of cultural mediators and the completion of all the screening procedures in a timely manner (9). In the case of migrants, the risk of reactivation of the latent infection once at destination is higher, due to a number of factors: living conditions (malnutrition or poor nutrition, poor hygiene), occupation, and accommodation (staying in closed, overcrowded, poorly ventilated and lit places). It is therefore necessary to pay attention to modifying those health determinants such as housing, reception, and work conditions that seem to be the real crucial factors in allowing immigrants to

Table 1 - Descriptive data for the refugees diagnosed with latent tuberculosis infection undergoing screening for hepatitis B virus (N=211).

Characteristic	HBV screening result		
	HBsAg +, HBcAb +	HBsAg -, HBcAb +	HBsAg -, HBcAb -
Age, median (95% CI)	22 (20-25)	25 (20-30)	23 (23-26)
Gender, n (%)			
Male	57 (98.3%)	56 (75.7%)	56 (70.9%)
Female	1 (0.7%)	8 (24.3%)	23 (29.1%)
Region of origin, n (%)			
Africa	55 (94.8%)	70 (94.6%)	70 (88.6%)
Burkina Faso	1 (1.7%)		
Cameroon		2 (2.7%)	
Ivory Coast	7 (12.1%)	16 (21.6%)	6 (7.6%)
Eritrea	1 (1.7%)		
Gambia	4 (6.9%)	6 (8.1%)	6 (7.6%)
Ghana	4 (6.9%)	4 (5.4%)	
Guinea	5 (8.6%)	2 (2.7%)	7 (8.9%)
Guinea-Bissau			1 (1.3%)
Liberia	1 (1.7%)		
Mali	8 (14%)	4 (5.4%)	1 (1.3%)
Nigeria	12 (20.7%)	26 (31.3%)	43 (54.3%)
Sierra Leone	1 (1.7%)	1 (1.3%)	
Togo	1 (1.7%)	2 (2.7%)	1 (1.3%)
Asia-Indo-Pakistan	3 (5.2%)	4 (5.2%)	9 (11.4%)
Bangladesh		3 (4%)	3 (3.8%)
Pakistan	3 (5.2%)	1 (1.3%)	6 (7.6%)
Total	58	74	79

maintain their state of health. On the other hand, facilitating the orientation of migrants suffering from infectious diseases towards the appropriate diagnosis and treatment paths, and ensuring that they are taken care of and avoiding stigmatization would make it possible to circumscribe possible infectious outbreaks, to the benefit of public health. In order to facilitate timely access to diagnosis and treatment, it is necessary to provide migrants - already in the first reception - with adequate information on the onset symptoms of tuberculosis and HBV and on how the infections are transmitted, paying attention to difficulties in language comprehension and adapting the content and form of messages to the cultural systems of reference (14-18).

Hepatitis B infection is highly prevalent in several areas of the world, notably Africa and Asia. The average prevalence of hepatitis B in migrants living in the EU that were born in an HBV prevalent country is 5.5%, compared to an overall prevalence of 1.12% in the general EU population (19). The epidemiological picture of hepatitis B in Italy over the last two decades has shown a strong decrease in both new infections and HBV marker prevalence. The annual incidence rate has decreased from 12.0 cases per 100,000 in 1985 to 0.6 in 2015 (20). Regarding the immigrant

population from countries with strong migration pressure, among the 3,915 cases of viral hepatitis B notified in the period 2004-2010, 16% involved foreign nationals (percentage increased from 13% in 2004 to 21% in 2013) (21). Also, the prevalence of hepatitis B is higher in migrants who were asylum seekers compared to all migrants (9.6% vs. 5.1%) (22). In Italy, incidence rates in foreigners remained around 4 per 100,000 until 2008, with a relative risk of 4 compared to the Italian population; then, from 2009, the distance between the two populations gradually narrowed, so that in 2011 the rates were 1.0 among Italians and 1.4 among foreigners (21). Since only a small proportion of the general study population (211/2,486) was screened for hepatitis B virus infection, it was not possible to extend the prevalence data to the whole sample and to directly compare it with other migrant cohorts, which showed a lower prevalence of HBsAg positivity (23-27). In a study by Nooredinvand et al. (28), the prevalence of hepatitis B virus and hepatitis C virus infection was assessed in active TB disease vs. LTBI patients. A minority (17.6%) of the individuals diagnosed with LTBI was HBcAb-positive and 3.4% was even HBsAg-positive. These are also very different percentages from ours, but it is essential to underline that the study was conducted in a general urban population. Our data, however, confirm previous observations that the prevalence of HBV infection in people with TB is higher than in the normal population (29-32). This observation supports the view that TST-positive individuals deserve a special attention with regard to hepatitis B screening, not only to avoid an unknown reservoir of untreated hepatitis B, but also because standard therapy drugs for TB infection are associated with significant side effects, the most serious being drug induced liver injury (DILI), which carries a fatality rate of up to 5% (33-35). Patients with unknown HBV infection are more susceptible to developing DILI and liver failure and having poor outcomes during anti-TB treatment (36-42). Unfortunately, this is not currently taken into account in the guidelines, but it is of particular importance and should be taken into account by decision-makers.

Regarding hepatitis B screening in recently arrived migrants, strategies recommended by guidelines and consensus conferences differ. In line with our proposal to offer HBsAg and HBcAb testing are the Health Protection Surveillance Centre (43) and Almasio et al. (44); various documents, while recommending screening, do not specify the procedures (45-47). However, it is worth noting that the assessment of HBsAg and HBcAb alone allowed us to uniquely identify HBsAg- and HBcAb-negative individuals as susceptible solely because no one reported previous HBV vaccination. As in many countries, especially in northern Africa, vaccination is offered on a more regular basis, the conjoint assessment of HBsAb remains the indication, in order to give a more complete picture of the HBV infection profile (48-51).

The importance of verifying how to deliver effective and cost-effective screening, vaccination, and health services to migrants is becoming crucial in a resource-constrained system. Regarding the cost-effectiveness of screening, Rossi et al. (22) note that, due to the higher prevalence of HBV infection among migrants from countries with high or intermediate prevalence, screening for chronic infection would be cost-effective even at 1% prevalence. In addition, qualitative studies suggest migrants would seek HBV screening to gain reassurance or to prevent liver disease (52, 53). However, in some groups there is a considerable lack of awareness of this infection, and fear of discrimination, stigma, and loss of income or social status may decrease uptake of screening and willingness to return for results and/or follow-up appointments (54). To be

as effective as possible, screening programs will need to be based on the involvement of local community partners, in order to gain their support. Alternatively, the strategy may be to carry out multi-disease testing at the point of first admission, offering one blood test for multiple infections in one appointment (55).

As far as vaccination practice is concerned, the fact that none of the refugees in our cohort reported a previous vaccination is significant and not encouraging. Unfortunately, vaccination coverage is still unsatisfactory in many countries. As of 2015, 185 (95%) countries had incorporated hepatitis B vaccination in the national infant immunization schedule, and 97 (49%) countries had introduced the recommended birth dose. In 22 (11%) countries, the hepatitis B birth dose was introduced only for infants born to HBsAg-positive mothers and, in 4 countries (2%), hepatitis B vaccine is provided only for specific risk groups or adolescents (56). However, a substantial burden of chronic HBV infection persists because the global coverage with the birth dose is still low, estimated globally at 39% in 2015 (57). The ad hoc expert panel of the ECDC guidelines reached a high level of agreement (87%) that hepatitis B screening and vaccination among migrants is a priority in the EU/EEA and that catch-up vaccination programs should be implemented (5).

Vaccination for HBV is recommended for minors (49, 51) and in all cases where susceptibility is established (43, 45, 48). In fact, the importance of screening for HBV infection relies not only on the identification of chronic infections, in the treatment and vaccination of contacts, and in health education, but also in the detection of negative individuals to be immunized. As recommended by the WHO, HBV vaccination is the most effective prevention strategy to reduce hepatitis B incidence and prevalence rate, especially in the population born after the implementation of measures that made HBV vaccination mandatory.

From the perspective of a comprehensive public health program, screening for HBV infection should lead to the extensive vaccination of negative individuals. Migrants often live in precarious hygienic conditions and have behaviors that expose them to greater risk (use of drugs, prostitution, etc.) of hepatitis B even during their stay in Italy. Limiting our approach to HBV screening on arrival only, without proposing vaccination in negative subjects, may be reductive and incomplete under a public health perspective. From their side, migrants, including refugees, have been shown to accept the value of hepatitis B vaccination (58). As for screening/vaccination strategies, they should be customized for the migrant/asylum seeker population in view of their characteristics and to maximize the effectiveness of the intervention, e.g. by concentrating multiple administrations in the same session whenever possible.

Limits

In addition to the limitations that were already discussed in the text, the authors would like to underline that the present study was not conceived to assess the cost-effectiveness of the intervention, and that the study population was limited to refugees and did not include economic migrants.

Conclusions

The prevalence of infectious diseases, such as latent tuberculosis and hepatitis B among migrants and refugees, is a major public health issue for the host country, due to the effects on the local epidemiology, not only in terms of spread of the infection but also in terms of long-term health, with the possible development of chronic morbidities. The importance of expanding screening

procedures in newly-arrived migrants has already been highlighted (24, 59). Systematic screening for HBV infection among migrants is likely to be cost-effective, even estimating low HBV prevalence, participation, referral, and treatment compliance (60). Furthermore, early detection of HBsAg-positive subjects could have important public health impact, if preventive measures such as education and vaccination of contacts and groups at risk (e.g. negative individuals) are implemented.

Riassunto

Screening per infezione da virus dell'epatite B nei rifugiati con diagnosi di tubercolosi latente in una comunità italiana

Premessa. I rifugiati sono una popolazione in costante aumento nell'area EU-27 e presentano esigenze di carattere sanitario specifiche che devono essere gestite nel modo più efficace e rapido possibile al loro arrivo. Lo screening per infezione da virus dell'epatite B viene offerto ad alcune categorie specifiche e potrebbe risultare utile ed efficace ampliarne le indicazioni. Lo scopo dello studio era di definire il profilo epidemiologico per l'infezione da virus dell'epatite B nei rifugiati ospitati presso i Centri per Richiedenti Asilo di Verona (Italia) con diagnosi di infezione tubercolare latente (latent tuberculosis infection) e che risultavano eleggibili per chemioprofilassi.

Metodi. Abbiamo effettuato uno studio retrospettivo in 715 rifugiati ai quali è stata fatta diagnosi di infezione tubercolare latente nel periodo 1 gennaio 2015 - 31 dicembre 2017. Lo screening per l'infezione da virus dell'epatite B è stato offerto ai pazienti prima dell'inizio del trattamento farmacologico. I soggetti sono stati testati per l'antigene di superficie del virus dell'epatite B (Hepatitis B surface Antigen) e per gli anticorpi per l'antigene core del virus dell'epatite B (Hepatitis B core antigen total antibodies). Nessuno dei pazienti screenati ha riferito una precedente vaccinazione per l'epatite B.

Risultati. Tra i 715 rifugiati con diagnosi di infezione tubercolare latente, 593 sono risultati eleggibili per il trattamento preventivo. Lo screening per l'infezione da virus dell'epatite B è stato accettato solo dal 35.6% (N=211) dei pazienti eleggibili per il trattamento. Centonovantacinque dei 211 (92.4%) provenivano da paesi africani e 16 (7.6%) dall'Asia; la maggioranza (80.9%) erano di genere maschile. L'età mediana era di 23 anni (95% CI 22-24). Dei 211, 58 individui (27.5%) sono risultati positivi ad antigene di superficie del virus dell'epatite B e anticorpi per l'antigene core del virus dell'epatite B; 74 (35.1%) negativi ad antigene di superficie del virus dell'epatite B e positivi ad anticorpi per l'antigene core del virus dell'epatite B; e 79 (37.4%) negativi ad antigene di superficie del virus dell'epatite B e ad anticorpi per l'antigene core del virus dell'epatite B. Il genere maschile e l'origine dal continente africano sono risultati associati ad una probabilità inferiore di risultare negativi ad antigene di superficie del virus dell'epatite B e anticorpi per l'antigene core del virus dell'epatite B.

Conclusioni. Lo screening per virus dell'epatite B è di fondamentale importanza non solo in termini di controllo e prevenzione dell'infezione, ma anche per problematiche sanitarie di lungo termine. Rendere lo screening più sistematico può avere un importante impatto in termini di sanità pubblica, nel rispetto della costo-efficacia e promuovendo la consapevolezza tra i gruppi etnici in modo da guardagnare la loro compliance ai programmi di trattamento e vaccinazione.

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