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Rational Diagnostics and Therapies in Child Refugees

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Violence, persecution, conflict and economic crisis have forced an increasing number of people to become displaced. According to the United Nations High Commissioner for Refugees, 10.3 million people were newly displaced in 2016, including 3.4 million refugees who sought protection abroad. By the end of 2016, a record number—22.5 million people worldwide—had become refugees, half of them children.[1]

Refugees, and in particular refugees under the age of 18, require specialized health-care services due to acute illnesses often acquired as a result of difficult living conditions, conditions of transit or inadequate prior management of chronic diseases. In addition to somatic diseases, refugees have an increased risk of mental health difficulties, including mood disorders, posttraumatic stress disorder, schizophrenia and nonaffective psychotic disorders.[2,3]

The top refugee hosting countries are low-income to middle-income countries with limited health-care resources. As political crises leading to forced displacement continue in different regions of the world, an increasing number of refugees arrive in European Union countries. Since 2015, European Union countries have taken in over 2 million refugees primarily from Syria, Iraq, Afghanistan and several African countries.[1] Refugee health has been intensively discussed among European health-care professionals. It has become evident that European health-care systems have difficulty providing adequate health care to the sharply increasing number of refugees. At the same time, hands-on initiatives led by individuals and groups of health-care professionals have been undertaken to improve health-care services to refugees in Europe.

The objective of this article is to summarize recent developments and to discuss controversial issues regarding rational diagnostics and therapies, with a special focus on infectious diseases in refugees under 18.

TUBERCULOSIS

In most European countries, the incidence of tuberculosis (TB) is low (<20/100,000 inhabitants). In contrast, refugees arriving in Europe often originate from countries with a high incidence of TB (>100/100,000), along with precarious living conditions that may further contribute to an increased risk of TB infection and disease. In a Swedish study, 6.8% of latent TB infection (LTBI) and 0.5% of active TB cases were reported in adolescent refugees from Afghanistan.[4] Among refugees from the Horn of Africa, approximately 30% had LTBI and 3.5% TB.[4] Different screening policies have been implemented in Europe. Some countries screen for TB disease via radiography, whereas other countries apply tuberculin skin testing (TST) and/or interferon-gamma release assays.[5] Many experts recommend LTBI screening in all child refugees even though universal LTBI screening has practical and ethical problems.[6] Children under 5 who are infected with *Mycobacterium tuberculosis* are at the highest risk of developing TB. It is therefore particularly important to apply LTBI screening in this vulnerable age group.[7]

Both TST and IGRA are imperfect screening tests. In general, TST is the preferred initial screening tool in children under 5 years old.[8] In children with positive TST results and/or in those with clinical suspicion for TB disease or known TB exposure, additional investigations should be conducted. Documentation of TST test results and test dates is particularly important. Repeat TST testing is often conducted among refugees as they move between countries. As a result of the booster phenomenon, this increases the likelihood of false-positive test results.[9] LTBI and TB disease should be treated according to World Health Organization (WHO) or national guidelines.[10]

HEPATITIS B

According to WHO, the prevalence of chronic hepatitis B infection is approximately 6% in the WHO African region and 3% in the WHO Eastern Mediterranean region.[11] A German study assessed the seroprevalence using antigens and antibodies against hepatitis viruses in 604 newly arrived refugees, including 15% (n = 91) of refugees under 18 years

Accepted for publication November 1, 2017.
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ISSN: 0891-3668/18/3703-0272
DOI: 10.1097/INF.0000000000001823

The ESPID Reports and Reviews of *Pediatric Infectious Disease Journal* series topics, authors and contents are chosen and approved independently by the Editorial Board of ESPID.

old. The overall seroprevalence of HBs antigen was 7.3% in refugees from Sub-Saharan Africa, and 4.9% and 2.5% in refugees from the WHO European and Eastern Mediterranean region, respectively. Among refugees <18 years, 41% had been vaccinated against hepatitis B.[12] Universal screening of all child refugees for chronic hepatitis B infection and hepatitis B virus immunity (serologic testing for anti-HBs and HBs antigen) is generally recommended because effective treatment options for chronic hepatitis B infection in children are available.[13] In addition, universal screening and subsequent immunization of unprotected children probably represent a cost-effective approach.[14] Under conditions where follow-up visits are not feasible, direct immunization without serologic testing should be considered.

HEPATITIS C

In the WHO eastern Mediterranean and European region, the prevalence rates of chronic hepatitis C infection are approximately 2.3% and 1.5%, respectively.[11] Among 604 refugees arriving in Germany, anti–hepatitis C virus was detected in 1.2%.[12] Children with chronic hepatitis C virus infection are usually asymptomatic and do not require immediate treatment. In addition, innovative hepatitis C treatment options, which are highly effective and well-tolerated in adult patients, have not yet been licensed for use in children and adolescents under 18 years. Therefore, both the Centers for Disease Control and Prevention and German pediatric societies have recommended against universal screening for hepatitis C infection in refugees under 18, unless they are members of high-risk groups such as children of hepatitis C virus–positive mothers.[15,16]

HIV INFECTION

HIV most severely affects patients from Sub-Saharan Africa, with nearly 1 in 25 adults being infected.[17] By contrast, HIV prevalence in most countries of the Eastern Mediterranean region is <0.2%.[17] A German study assessing HIV seroprevalence in newly arrived refugees found that HIV antibodies were detected in 0.25% (2/789) of all refugees tested. Both infected individuals originated from Sub-Saharan African countries.[18]

Because HIV-positive children clearly benefit from the early initiation of a highly active antiretroviral treatment, German and Swiss pediatric societies have recommended that screening for HIV antibodies be offered to refugees under 18 who originate from Sub-Saharan African countries.[7,15]

SCHISTOSOMIASIS

Intestinal and urinary schistosomiasis is a major, and often-neglected, tropical disease. Schistosomiasis mainly, although not exclusively, affects residents of Sub-Saharan African countries. Among young adult refugees from Sub-Saharan Africa, seroprevalence rates of 28% (103/373) have been reported. The rate of positive microscopy was 17% (65/373).[19] Similarly, a German study showed positive serology results in 25% (448/194) of unaccompanied refugees under 18 from African countries.[20]

Chronic schistosomiasis is often clinically asymptomatic for years, but it nevertheless can result in a considerable long-term morbidity. Related symptoms include anemia, stunted growth, impaired cognition and decreased physical fitness, as well as organ-specific effects such as periportal fibrosis and chronic urogenital inflammation with an increased risk of malignant degeneration.

While praziquantel is available as a safe, effective and inexpensive treatment option for schistosomiasis, screening for the disease is hampered by the lack of a fast and reliable gold standard diagnostic test. Microscopy of urine and stool samples conducted by experienced personnel is highly specific, but its sensitivity is limited and microscopic assessment of urine and stool samples is not feasible as part of routine screening. The use of peripheral eosinophilia is also hampered by its low sensitivity.[21] Immunochromatographic test assays can be conducted in point-of-care settings and appear to be the best choice for schistosomiasis screening. A recent study reported an excellent test sensitivity of 96% for a commercially available immunochromatographic test assay in serum samples from African migrants.[22]

In our opinion, all refugees originating from or having traveled through endemic areas in Sub-Saharan Africa and/or along the Nile River should be screened for schistosomiasis. From an implementation perspective, applying a rapid immunochromatographic assay seems pragmatic. Positive rapid test results should ideally be confirmed by a second test. Under conditions where reevaluation is not possible, individuals with positive test results should be promptly treated with praziquantel.

OTHER HELMINTHIC INFECTIONS

In general terms, little information is available on the prevalence of helminthic infection in child refugees. A recent study from Sicily, which primarily included young male adults from African countries, investigated the prevalence of geohelminthic infections in a single stool sample. Geohelminthiasis was reported in 11% (30/274) of participants.[23] *Ancylostomatidae* was the most common infection (n = 10), followed by *Trichuris trichiura*, Taenia spp., *Schistosoma mansoni*, *Dicroelium dendriticum* and *Strongyloides stercoralis*.[23] Coproparasitological sampling and assessment of stool samples is, however, difficult to obtain. In addition, currently there is no information available on the disease burden of helminthic infection in refugees under 18 from Asian countries or from countries in the Near East and Middle East. Data on cost-effectiveness of antihelminthic prophylaxis in refugees under 18 are also lacking. For these reasons, German pediatric societies have not recommended universal coproparasitological screening in refugees under 18.[15] Nevertheless, parasitological assessment should be initiated in refugee children who display clinical symptoms of helminthic infections and who have persistent eosinophilia. A cutoff value of >450 eosinophils/μL is recommended by the Spanish Society of Tropical Medicine and International Health.[24] In our experience, however, a cutoff of >1000 eosinophils/μL produces fewer negative follow-up results without missing too many helminthic infections that otherwise would have required treatment (unpublished data).

MULTIDRUG-RESISTANT BACTERIA

Many refugees originate from or travel through regions with a high prevalence of multidrug-resistant bacteria. This not only includes regions such as Afghanistan, the Near East, the Middle East and North Africa, but also includes transit countries such as Turkey and Greece. In one children's hospital in Germany, multidrug-resistant organisms were detected in 34% (110/325) of hospitalized refugee children.[25] Another study collected stool samples from mainly healthy refugees under 18 arriving in Frankfurt am Main, Germany.[26] This study detected *Enterobacteriaceae* with extended-spectrum beta-lactamases in 35% (42/119) of patient samples.[26] Both of these studies mainly included children originating from Syria and Afghanistan. Pediatricians in low-endemicity countries should be aware of this high prevalence rate of multidrug-resistant organisms in refugee children. On the basis of available data, screening for multidrug-resistant organisms seems to be justified in hospitalized refugees under 18.

CONCLUDING COMMENTS

Developing a universally applicable screening program for refugees under 18 is challenging. Epidemiologic data on the disease burden in child and adolescent refugees are dependent upon a variety of factors, including geographical origin of the refugee, duration and route of flight, living circumstances before and during transit, underlying diseases and the quality of prior medical treatment. Legal requirements and health-care

resources also need to be accommodated as part of any screening program. Standardization of screening programs within the European Union would be helpful for the purpose of guiding national or regional screening programs, but in practice, each program still will need to be adapted to local needs by local health-care providers. Across regional and national boundaries, the cooperation of health-care providers is needed for the purpose of coordinating health-care activities and to avoid unnecessary and expensive repetition of screening tests. A centralized, online-based, Europe-wide patient data collection system urgently needs to be developed. As a prerequisite, legal issues with data privacy need to be addressed and solved. Doing so will require substantial financial and logistical support from European governments, but the endeavor is critical not just for the improved medical care of child and adolescent refugees in Europe, but also for public health more generally.

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