- **1** Providing medical care for migrant children in Europe:
- 2 a practical recommendation
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- 33 Abstract (200 words max)
- 34

35 Between 2015 and 2017, an estimated 200,000 to 400,000 children were seeking asylum each 36 year in EU/EEA countries. As access to high-quality health care is important, we collected and 37 compared current recommendations across Europe for a consensus recommendation on 38 medical care for migrant children.

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40 Existing recommendations were collected from published literature and identified through 41 national representatives from paediatric societies of 31 EU/EEA countries. In addition, 42 guidelines from Australia, Canada, and the United States were reviewed. Evidence on 43 recommendations to be considered for inclusion was specifically identified in literature 44 searches focused on recent evidence from Europe.

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46 For eight EU/EEA countries a national recommendation was identified. Growth and 47 development, vision and hearing impairment, skin and dental problems, immunisations, 48 anemia, micronturient deficiency, helminths, hepatitis B and C, human immunodeficiency 49 virus, malaria, schistosomiasis, syphilis, tuberculosis, posttraumatic stress disorder and sexual 50 health were most frequently mentioned and therefore selected for inclusion in the 51 recommendation.

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53 Conclusion:

54 The current document provides recommendations based on expert opinion and evidence for 55 medical care for migrant children in Europe. These include general topics on ethical standards, 56 use of interpreters, follow-up and documentation and specific recommendations for 57 communicable and non-communicable conditions and diseases.

- 58
- 59 **Keywords**
- 60 ;

- 62 Background
- 63

64 Countries in the European Union (EU) and European Economic Area (EEA) continue to be challenged by the health needs of asylum seekers and refugees. In recent years an 65 66 unprecedented high number of children and adolescent were seeking asylum in EU countries 67 [133]. In 2017 over 200,000 children and adolescents claimed asylum adding to an estimated 68 800,000 children and adolescents that arrived in 2015 and 2016 [135]. Although there is 69 considerably heterogeneity in the demography of asylum seekers and refugees across Europe, 70 children are estimated to make up over 30% of all asylum seekers. In 2016 and 2017, most 71 asylum-seeking children and adolescents in the EU and EEA originated from the Syrian Arab 72 Republic, Afghanistan and Iraq [135; 136]. Germany remained the top destination for asylum-73 seeking and refugee children and adolescents but high numbers were also recorded in France, 74 Greece, Italy, Austria, Sweden, the United Kingdom, Spain and Switzerland [135].

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76 Access to high-quality health care is important for migrant children as they have specific health 77 risks and needs. All countries in the EU/EEA have signed the United Nations Convention on 78 the Rights of the Child, which implies that migrant children, regardless of their legal status, 79 have the right to health care of the same standard as non-immigrant children [134]. In almost 80 all countries in the EU/EEA, a health assessment is recommended in newly settled migrant children [55]. The terminology including "health assessment", "health screening" and 81 82 "medical examination" as well as the systematic voluntary or mandatory use thereof varies 83 widely [56]. The main aim of such a health assessment is similar in all countries and focuses 84 on both the identification of individual health needs in the migrant population and the 85 prevention of health risks for the resident population.

86

Meeting the health needs of migrant children in Europe is important as this is a particularly 87 88 vulnerable group and paediatricians therefore play a unique role. In Canada, the United 89 States, and Australia, paediatricians are guided by national recommendations for the care of 90 migrant children [21; 109; 130]. In Europe, the European Commission has issued a handbook 91 for health professionals on the health assessment of refugees and migrants in the EU/EAA 92 [63]. This protocol has been tailored for the early health assessment at reception centres or organised hotspots to identify significant medical conditions that impact on placement in 93 hosting institutions and fitness for travel. Only few European countries have national 94

95 guidelines for primary care for migrant children. The European Academy of Paediatrics (EAP) 96 initiated a survey of existing recommendations and has facilitated a group of experts to 97 complie recommendations providing primary care for migrant children in a European host 98 country. The current document is based on existing national recommendations, expert 99 opinion and limited evidence. It provides a practical apparoach aimed at the identification of 100 health needs and medical care for migrant children in Europe.

101

#### 102 Methods

#### 103 Data collection

104 Current existing clinical guidelines and recommendations on the management of migrant 105 children in the EU/EEA were collected and compared. Representatives from national 106 paediatric societies from 30 EU/EEA countries were approached by email between 1 107 December 2016 and 1 June 2017 in which they were asked to provide the working group with 108 their national guideline or recommendation for the medical care of migrant children. Data 109 were collected from these national clinical guidelines and from published non-European 110 recommendations from Canada, the United States and Australia [18; 21; 109]. 111 Recommendations for all diseases and conditions were systematically extracted and collected 112 in a database; those mentioned in at least one of the national recommendations were 113 evaluated for inclusion into the recommendation.

114

#### 115 Definitions

There is no universally accepted definition of a migrant, therefore for this manuscript, the definition of "migrant children" put forward by the International Society for Social Pediatrics and Child Health was used [45]. Briefly, "migrant children" refers to children and adolescents less than 18 years of age who are on the move or have settled in other country and who experience unfavourable conditions including exposure to war and other forms of violence, socioeconomic deprivation and limited access to health care and education.

122

#### 123 Writing process of the recommendation

124 The core writing group, including two primary care paediatricians (SdT and CW), one 125 paediatric infectious diseases specialist (NR) and a paediatric registrar and clinical 126 pharmacologist (LS), selected and discussed the diseases or conditions that were mentioned

127 in at least 7 out of 11 of the included guidelines. Then, for each disease (indicated with an\*), 128 a literature search for recent data specific to migrant populations particularly in Europe and 129 indirect evidence from other populations was done. A systematic literature search for each 130 topic was beyond the feasibility for this recommendation and therefore emerging evidence from planned systematic literature searches will be important for updates of this 131 132 recommendation [110]. Relevant evidence was classified according to the Grading of 133 Recommendations Assessment, Development and Evaluation (GRADE) for quality of evidence 134 and strength of recommendation (supplementary material Table 1 & 2). During the 135 discussions, a balance was sought between the quality of the evidence, potentially desirable 136 and undesirable effects of screening or intervention, practical issues and costs.

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#### 138 Availability of national recomendations

Responses were received from representatives of all 31 countries (100% response rate).
National representatives from eight countries (Austria, Finland, Germany, Italy, Spain,
Switzerland, United Kingdom, and the Netherlands) reported to have a national guideline or
recommendationt that included the primary care management of migrant children and
adolescents. All were available as online resources and/or published articles [3; 8; 28; 38; 39;
43; 85; 96; 97; 117]. National representatives from 23 European countries reported that there
was no national recommendation available or that they were not aware of such a document.

147 Conditions covered in at least one of the national guidelines are summarised in the table 1.

Of these, growth and development, vision and hearing impairment, skin and dental problems, immunisations, anemia, micronturient deficiency, helminths, hepatitis B and C, human immunodeficiency virus (HIV), malaria, schistosomiasis, syphilis, tuberculosis, posttraumatic stress disorder and sexual health were mentioned in at least 7 out of 11 guidelines and therefore selected for further evaluation and inclusion into the recommendation.

#### 153 **Recommendations**

### Recommendation 1: Check if the migrant child is accompanied by at least one parent or a legally responsible caregiver.

If not, find out if the child has a caregiver. If the child has an adult caregiver, ask the child to return for another appointment with the responsible caregiver and contact social workers to help the child or adolescent to achieve this. For unaccompanied children, some countries have a system in place of legal advisors.

154 Migrant children – as all children - should not be held solely responsible for managing their 155 health. While their right to participate in their health care should be respected during all visits, they should be provided with care in the presence and with the assistance of an adult who is 156 157 legally responsible for their care, and who is able to make health decisions on their behalf, if 158 necessary. If a child arrives for a health visit unaccompanied by a caregiver or legal advisor, 159 health workers should determine if there is an adult who is responsible for their care. If the 160 child has an adult who is responsible for them, the child should be given a new appointment 161 and the health services should ensure that the caregiver is informed about the new 162 appointment and is able to accompany the child for the return visit.

- 163 Children who are identified as separated or unaccompanied require special protection [45]. In 164 such circumstances the relevant social services should be notified and brought in to assist in 165 the reception and care of the child.
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### Recommendation 2: Check if the parent/carer is capable to communicate sufficiently; access professional interpreter services if limited language proficiency is suspected (Grade C).

Professional interpreter services including face-to-face, telephone or video services are available in many countries. If not available, ask the migrant child and family to return for another appointment together with a person able to interpret and/or contact social workers to ensure this and defer the following recommendations preferably to a next appointment.

167 It is essential to ensure good communication between health care professionals and migrant 168 children and families to deliver appropriate and effective care [11; 66]. Language barriers 169 between patients and providers have been shown to reduce the level of health care and 170 increase the risk of adverse events and fatal outcomes [10; 30; 112]. In a European-wide 171 survey amongst paediatric accident and emergency staff, more than 2/3 reported language 172 and translation issues being one of the most critical barriers in providing care to migrant 173 children (RefuNET survey, personal communication from Ulrich von Both, 1<sup>st</sup> November 2017). 174 Assessment of language proficiency is not trivial, and the requirement of an interpreter may 175 only become evident during the encounter. The use of professional interpreters has been 176 demonstrated to reduce these risks by improving the quality of translations and reducing 177 unnecessary diagnostics and treatments; furthermore, professional medical interpreters 178 reduce the cost of care and increase patient satisfaction with the performance of health care 179 professionals [11; 35; 37; 52]. Therefore, medical interpreters and cultural mediators should 180 be made available during language-discordant health care encounters, [63; 95] and adequate 181 time should be allocated for these encounters [44]. Face-to-face interpreters are generally 182 preferred by both European and non-European migrants [48-50; 60].

183

184 Another important aspect of care relates to the provision of culturally-sensitive health 185 information. [44]. This may include signposts that are adapted by using pictograms or colour 186 codes, as well as translated leaflets with information about specific health topics [45]. The 187 ICOON picture dictionary may be helpful as a first communication tool 188 (http://icoonforrefugees.com). This tool includes over 2,000 generic icons and photos, 189 including those specifically focused on health and health care issues in migrants.

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### Recommendation 3: Ask about health problems that the parents and the children themselves identify. (Grade D).

191 To get familiar with the situation of the migrant children and their families a few simple but 192 important questions may be asked at the outset of the consultation. A mnemonic list for this 193 is suggested in **Table 2**. It is however important that migrant children may present with a wide 194 range of health problems not necessarily relating to their migrant background [108]. The 195 heterogeneity of the migrant population is large, and several factors considerably influence 196 previous care and current health requirements. The focus of the initial primary care health 197 assessment should therefore be to identify individual health needs. However, it is also 198 important to acknowledge that health literacy and the concept of preventative health

- 199 measures may be limited and therefore the following recommendations can be used as a tool
- 200 in the dialogue with the family to identify individual requirements.
- 201

Recommendation 4: Ask about growth\* and development\* and perform a physical evaluation including asssement of weight-for-age and height-for-age, development and vital parameters. Be alert for signs of congenital anomalies\* (i.e., heart defects), non-communicable (developmental delay and tumours) and infectious diseases (hepatosplenomegaly and lymphadenopathy) (Grade C-D).

202 Evaluation of growth and development are part of routine assessments in primary care 203 paediatrics. In the country of origin, migrant children may have not been followed regularly 204 and important reasons for growth or development disorders may have gone unnoticed. Both 205 malnutrition and overweight/obesity are prevalent in many countries of origin of migrant 206 children. Studies indicate that newly arriving migrant children have a higher prevalence of 207 growth abnormalities particularly reduced weight-for-age and height-for-age [121; 123]. Moreover, migrant children from countries in North-Africa show increasing levels of childhood 208 209 obesity particularly after resettlement to Italy [23; 46; 47]. This has also been shown for other 210 migrant populations in other countries including Switzerland and Austria [42; 66; 72]. Contrary 211 to this, in a study in unaccompanied adolescent migrants in Germany normal body mass index 212 was found [82]. Importantly, as migrant children have anthropological differences due to 213 genetic background appropriate adjusted percentiles and values for growth and development 214 are required [46; 53].

215

Migrant children are at risk for developmental delays, but standardized developmental screening may be challenging. The Parents' Evaluation of Developmental Status (PEDS) or the handbook for health professionals on the health assessment of refugees and migrants by the European Commission may be used as a developmental tool in migrant-focused paediatric primary care, particularly when linked with appropriate interpretation services [61; 63; 73].

221

Congenital heart disease accounts for nearly one-third of all major congenital anomalies. The
 reported birth prevalence has increased substantially over the last century, reaching a stable
 estimate of 1.35 million new-borns with congenital heart disease every year, with the highest

225 reported birth prevalence in Asia [138]. The frequency of previously undetected and/or 226 untreated congenital heart defects in migrant children is unknown but has been described 227 both in refugee camps and hospital-admitted migrant children [2; 108]. Other non-228 communicable diseases may be more common. In 2015, 13% of hospital-admitted migrant 229 children in a University Hospital in Switzerland had a previous medical condition, including 230 diabetes mellitus type 1, leukemia, and seizure disorder [108]. Infections both acute and 231 chronic are the most common disease affecting up to 60% of migrant children [82; 100; 118; 232 131].

233 Vision loss and undiagnosed sight-threatening eye disease may be more common in migrant

## Recommendation 5: Ask for vision\* and hearing problems\*, perform a routine vision and hearing screen (Grade D).

234 children, since hearing and vision impairment are major causes of disability worldwide [29]. 235 However, current evidence on the frequency of vision and hearing abnormalities in migrant 236 children is lacking. Evidence from adult refugees suggests that both vision and hearing 237 impairment are common [146]. In addition, late identification of hearing problems may have 238 serious consequences, including poor social-emotional and cognitive development, delayed 239 speech and language acquisition, and poor academic performance [93]. If age-appropriate 240 screening suggests vision or hearing impairment it is recommended to refer the child to 241 specialist further evaluation.

242

Recommendation 6: Examine the entire skin and oral cavity and be alert for signs of infections (including scabies, impetigo)\*, malnutrition and micronutrion deficiency\*, tooth decay\*, and scars\* (Grade B-C).

243 Infectious skin and soft tissue diseases are among the most frequently encountered health 244 problems of newly arrived migrants in Europe. Poor hygienic conditions during their travel and 245 in the country of arrival can lead to skin infections. Scabies has been reported in 3% of 246 unaccompanied adolescent migrants in Germany and skin problems were one of the most 247 common physical findings in young migrants in Croatia [82; 84]. Another rare but potentially 248 life-threatening skin infection is cutaneous diphtheria, which manifests as chronic skin ulcer 249 and is increasingly found in migrants in Europe [88]. Poor nutritional status and micronutrient 250 deficiency are also common in studies of migrant children and particularly results in vitamin

D deficiency including severe rickets and iron deficiency (see also below) [24; 118; 122]. Furthermore, migrant children are routinely suffering sexual violence, exploitation, abuse and detention; therefore the skin should be examined carefully for scars [133].

254

Worldwide, oral conditions affect 3.9 billion people, with untreated caries in permanent teeth 255 256 being the most prevalent condition, especially in Oceania, South Asia, North Africa/Middle 257 East and West, Central and Southern Sub-Saharan Africa [81]. Migrant children may have 258 increased rates of dental caries due to inadequate dental care in the country of origin [65]. In 259 unaccompanied migrant adolescents in Germany, pathological dental status has been 260 reported in 20% of adolescents, especially in Sub-Saharan and Northern African migrants [82]. 261 The involvement of paediatricians can facilitate the promotion and prevention of dental 262 caries. In addition, early detection and referral helps to avoid surgical interventions [100]. 263 Therefore, dental health should be evaluated and referral to a dentist should be arranged as 264 appropriate.

265 Migrant children may be susceptible to vaccine-preventable diseases upon arrival in Europe,

### Recommendation 7: Check immunisation status and - if unknown or incomplete - start catch-up immunisations according to national recommendations as soon as possible.

due to barriers in access to preventive care in their country of origin and during their period of travel, which may last up to years [45; 91]. Data on vaccination coverage of migrant children in Europe are limited, but coverage is likely to be variable. In Switzerland, only 27% of newly arriving migrant children had antibodies against diphtheria-tetanus-pertussis consistent with previous vaccination [26]. In Germany, migrant children appear to be at higher risk to be unvaccinated for measles, mumps, rubella, and varicella with only 69% of children and adolescents being immune [64].

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In addition, in Germany the vaccination coverage for poliovirus has been estimated to be less
than 15% among migrant children from Syria [12] and vaccination against hepatitis B virus in
school age children was more often incomplete among migrant compared to native children
in Germany and New Zealand [90; 118].

278

Although it is possible to perform pre-vaccination screening for specific antibodies, this approach is costly and generally not recommended. Antibody concentrations as correlates of protection are standardised in the situation of known previous immunisation and poorly understood in the situation of unknown previous immunisation as in most migrants. As national immunisation schedules vary across Europe; catch-up immunisations should be started according to the national recommendations.

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### Recommendation 8: Treat intestinal parasites\* empirically in all children > 2 years and > 10 kg with one dose of 400 mg albendazol (Grade B).

287 Migrant children are at risk for contracting an intestinal infection with parasites due to 288 repeated exposure to endemic parasitic diseases in their country of origin and conditions 289 during their journey. A study of 247 migrant children in Italy found that children older than 5 290 years of are more likely infected with intestinal parasites compared to non-migrant children 291 [79]. Studies in Germany and Spain found the prevalence of parasitic infection among both 292 unaccompanied and accompanied children as high as 20% [82; 124]. Intestinal helminth 293 infections with moderate to heavy worm burdens can lead to malabsorption and chronic 294 blood loss, with potential long-term effects on growth and development [71]. Evaluation of 295 stool for gastrointestinal infections is logistically challenging and requires evaluation of one to 296 several specimens for adequate sensitivity [13]. As such, stool analysis should be considered 297 for selected cases only including persistent symptoms after empiric treatment. Empiric 298 treatment with albendazole is inexpensive, of short duration, and has been shown to be highly 299 effective with a favourable safety profile in children older than 2 years of age [128]. The 300 recommended dose for albendazole for children > 2 years and > 10 kg is 400 mg as a single 301 dose [119; 145]. Of note, safety data for children in the first two years of life is limited. Some 302 authors recommend 200 mg as a single dose for children aged 12-23 months [145]. 303 Albendazole should not be used in pregnant adolescents and in patients who have symptoms 304 and/or a travel history compatible with neurocysticercosis.

#### **Recommendation 9: Take a blood sample to measure** a) hemoglobin to check for anemia\* and treat iron defiency\* if present (Grade B) b) HBV\* (Hbs-Ag, anti-Hbs and anti-HBc) (Grade B) For HBV hepatitis B surface antigen (Hbs-Ag), the antibody to hepatitis surface antigen (anti-Hbs) and the antibody to hepatitis B core antigen (anti-HBc) should be used to differentiate between acute, resolving and chronic HBV infection. ADD (all Grade C-D) c) If dark skin, covering clothes or Vitamin D\* signs for nutrional rickets: d) If from sub-Saharan Africa: Schistosomiasis\* serology and CCA urine test e) If from sub-Saharan Africa or known risk: **HIV\*** serology or PCR f) If febrile: Malaria\* screen g) If immunosuppression isknown or forseen: Strongyloides\* serology Syphilis\* serology h) If sexually active or abused:

#### OPTIONAL

i) HCV \*(Grade D)

306

#### 307 Anaemia and iron deficiency

308 Iron-deficiency anaemia is the most common cause of anaemia and the most common 309 nutritional disorder worldwide [69]. Young children are among the most affected and it is 310 estimated that worldwide 43% of all children younger than 5 years of age have iron-deficiency 311 anaemia [127]. Most migrant children originate from regions with higher prevalence of acute 312 and chronic malnutrition and higher rates of communicable diseases, including intestinal 313 helminth infections. Detection of iron-deficiency anaemia is important, as it may lead to 314 impaired physical and cognitive development and iron supplementation improves mental 315 development in children [86; 120]. Anaemia prevalence amongst migrant children has been

316 found to vary widely, ranging from 13% to 49% across different countries and settings [9; 82; 317 106; 108; 121; 126]. While the reason for anaemia is often not identified, iron deficiency is 318 likely the main cause [106; 121]. Diagnostic measures to confirm iron-deficiency anaemia 319 include serum ferritin and haemoglobin, or haematocrit response to iron administration. 320 Other causes of anaemia, such hemoglobinopathies or haemolytic anaemia may coexist with 321 iron-deficiency anaemia but are less commonly found in migrant children [118]. In several 322 countries in North-Africa and Sub-Saharan-Africa, the Middle East and West Asia, prevalence 323 of thalassemia and sickle cell disease is high. In sub-Saharan African migrants in Spain, sickle 324 cell disease and glucose-6-phosphate dehydrogenase deficiency were identified in 18% and 325 15%, respectively [74]. In the Netherlands, 6% of migrant children had anaemia due to 326 thalassemia [126]. If hemoglobinopathy is suspected, a haemoglobin electrophoresis should 327 be done.

328

#### 329 Hepatitis B virus infection

330 Hepatitis B virus (HBV) is the most common cause of hepatitis worldwide, with prevalence in 331 children reported up to 10% in certain Western sub-Saharan countries [101]. The prevalence 332 of HBV infection in Europe is estimated to be around 1% (range 0.1% to 4.4%) in the general 333 population, and lower in children [1]. In Europe, migrants from East Asia, the Pacific and Sub-334 Saharan Africa have the highest seroprevalence of chronic HBV infection, followed by migrants 335 from Eastern Europe and Central and South Asia [25]. In sub-Saharan African migrants in 336 Spain, 15% were HBsAg positive [124]. The prevalence of Hepatitis B infection has been found 337 to be highly variable among migrant children in Europe and reaching as high as 10% in 338 undocumented migrants in Italy [16; 20; 72; 92]. Migrant children benefit from screening and 339 treatment of HBV infection to prevent hepatitis and hepatocellular carcinoma since the risk of 340 developing chronic HBV infection is up to 50% of children infected before age 5, and as many 341 as 90% infected at birth go on to develop chronic infection [31; 109; 116]. In addition, there is 342 evidence that screening migrants for HBV is cost effective [51; 67].

343

#### 344 Vitamin D deficiency

Accumulating global reports indicate that vitamin D deficiency (in the following defined as 25-OH-vitamin D levels < 25 nmol/l) is a widespread and major health problem, particularly in middle Eastern countries [104]. There are few studies on vitamin D screening in migrant 348 children. In a Norwegian study 17% to 58% of the girls and 4% to 23% of the boys had vitamin 349 D deficiency, with greater prevalence among adolescents and in children from Iraq and Afghanistan [32]. An Australian study in Afghan migrants found that 23% were vitamin D 350 351 deficient [122]. Children with Vitamin D deficiency are at risk of developing osteomalacia and 352 nutritional rickets, however not all children develop symptoms [94]. Clinicians should 353 therefore be attentive for the following signs: swelling of ankles and wrists, delayed (> 2 years 354 of age) closure of the fontanelle, delayed tooth eruption (lack of incisors by 10 months or 355 molars by age 18 months of age), leg deformity, delayed gross motor development (crawling 356 and walking), failure to thrive, and muscular weakness [94]. As general vitamin D screening in 357 migrant children is unlikely to be cost-effective, only children with risk factors or signs 358 suggestive of symptomatic vitamin D deficiency should be tested [4; 32]. For prevention of 359 vitamin D deficiency, national recommendations should be followed. For treatment of 360 nutritional rickets generally daily doses of 2000 to 6000 IU/day (depending on age) for a 361 minimum of 3 months together with 500 mg/day oral calcium per day are recommended [94]. 362 Single high dose treatment may be an alternative and appropriate dose recommendation can 363 be found in the global consensus recommendations on prevention and management of 364 nutritional rickets [94].

365

#### 366 Schistosomiasis

367 Schistosomiasis is rare in Europe, and is mainly imported from endemic countries due to 368 traveling or human migration [54]. In Germany, two studies in unaccompanied adolescent 369 migrants showed that schistosomiasis was present in individuals with sub-Saharan Africa 370 origin in approximately 25% [82; 131]. A recent study in adolescent and young adult Eritrean 371 refugees in Switzerland showed an even higher prevalence of schistosomiasis of almost 60% 372 [19]. Lower prevalence was seen in Spain and Canada, where 9% to 15% of sub-Saharan 373 African migrants had evidence of schistosomiasis [124]. In contrast, unaccompanied 374 adolescent migrants from Syria, Middle East and North Africa had a low prevalence of positive 375 schistosomiasis serology of < 2% [92; 131]. The two main Schistosoma species are S. mansoni 376 causing intestinal and S. haematobium causing urogenital disease. Undiagnosed and chronic 377 schistosomiasis may lead to hepatic fibrosis, portal hypertension, hypersplenism, ureter and 378 bladder fibrosis, hydronephrosis and bladder cancer. Serologic testing is the most sensitive 379 diagnostic modality for S. haematobium and for S. mansoni . In addition, a recently introduced

low cost point-of-care test called circulating-cathodic-antigen (CCA) may also be used if
 available [19; 54]. If serology or CCA test are positive, referral to a practitioner experienced in
 the diagnosis and treatment of schistosomiasis is recommended.

383

#### 384 Human immunodeficiency virus infection

385 More than 95% of individuals with HIV infection reside in developing countries, two-thirds of 386 them in sub-Saharan Africa. In Europe, between 1999 and 2006, more than half of patients 387 with HIV in Europe were migrants, largely from Sub-Saharan Africa [27]. Migrant children from 388 countries where HIV is endemic are at risk for HIV infection via mother-to-child transmission 389 [78]. The prevalence of HIV among migrant children varies based on risk factors from their 390 home countries, during the journey, and after arrival. Studies in Germany and Italy have found 391 HIV prevalence of 0.4% and 1.7% in migrants, respectively [20; 72]. In Canada, 1% of HIV-392 infections were seen in migrant children below 15 and 2% in those over 15 years of age [113]. 393 HIV infection in children older than 18 months can generally be diagnosed by serology, 394 although serological test can be falsely negative during the early course of the infection, when 395 the antibody response has not yet fully developed. In infants and children younger than 18 396 months, in whom antibody tests are not reliable because of the persistence of transplacentally 397 acquired maternal antibodies, DNA or RNA assays are required. Rapid point-of-care antibody 398 screening tests may be performed for convenience and/or costs; however, consent and 399 appropriate pre- and post-test counselling should be performed. Any positive HIV ELISA or 400 rapid test always requires confirmatory testing by either Western blot or molecular methods. 401 If two-tier testing reveals HIV diagnosis, the child needs to be referred to a paediatric 402 infectious disease specialist for appropriate treatment and futher evaluation.

403

#### 404 Malaria

More than 90% of malaria cases and 92% of malaria deaths occur in sub-Saharan Africa, mainly in children younger than 5 years [143]. Imported malaria is most often seen in migrants and returning travellers who did not use adequate preventive measures. Despite this, malaria is rarely detected in asymptomatic migrant children. Only 1-2% of unaccompanied minors in Germany and Spain from sub-Saharan had malaria and in a study in migrant children in New Zealand only one case was detected in 5 years [82; 118; 124; 131]. Compared to adults, children with malaria are more likely to present with non-specific symptoms including fever,

412 lethargy, malaise and with gastrointestinal symptoms [22]. Children may also have 413 hepatomegaly, splenomegaly and jaundice, and are more likely to have fever greater than 414 40°C [22]. The value of routine screening for asymptomatic malaria is unknown and the 415 characteristics of malaria screening tests in asymptomatic individuals is uncertain. Therefore, 416 the recommendation is to focus on timely diagnosis and treatment of symptomatic malaria.

An important but rare differential diagnosis in this context, especially in patients originating from the Horn of Africa, is louse-born relapsing fever, an infection caused by *Borrelia recurrentis* [57; 140] The diagnosis for both malaria and louse-born relapsing fever is usually made by microscopic examination of thick and thin blood films, which should be requested urgently in any febrile migrant child from malaria-endemic areas (which includes but is not limited to sub-Saharan Africa, Pakistan and Afghanistan).

423

#### 424 Strongyloides

425 Strongyloides stercoralis, an intestinal parasitic nematode, is increasingly detected, especially 426 in Southern, Eastern and Central Europe, the Caribbean, in Southeast Asia, Latin America, and 427 sub-Saharan Africa with reported prevalence up to 50% [111]. Migrants from Southeast Asia 428 and Africa have the highest risk of infection [14; 17; 36] as has been seen in young migrants in 429 Spain showing a prevalence of 28% of strongyloides infection [75; 124]. Subclinical infection 430 or low-grade disease can persist for decades after migration and in the presence of 431 immunosuppression may progress into life-threatening disseminated disease [15; 41]. 432 Serologic testing is the most sensitive diagnostic modality to detect strongyloides as stool 433 microscopy for ova and parasites has low sensitivity [15]. Testing is recommended particularly 434 for immunocompromised individuals or before initiation of immunomodulatory treatment.

435

#### 436 Syphilis

Syphilis is most common in Sub-Saharan Africa, South and Southeast Asia, and South America [142]. Beyond the neonatal period, sexual contact is the primary means of transmission of syphilis [141]. In a health centre in Spain, 6.4% of all migrants had a positive syphilis serology whereas in Malta, latent syphilis was found in 2,2% of adult migrants [80; 102]. Literature on the prevalence of syphilis in migrant children in Europe is lacking, however it is known that migrant children are at increased risk of violence and sexual abuse [133]. Data from migrant children and adults seen in primary care clinics in Canada suggest syphilis is rare (< 1%) in

migrant children [141]. Children often have few dermal findings like chancre [76]. Therefore,
asymptomatic children may only be identified by screening. Antibody tests like the Venereal
Disease Research Laboratory (VDRL) test are used for initial screening because of their
relatively low cost, ease of performance, and ability to be quantified for following therapy
response. However, they are nonspecific and require confirmation by specific tests [141].
Children diagnosed with syphilis should also be evaluated for other sexually transmitted
diseases and screened for exposure to sexual exploitation, violence and trafficking.

451

#### 452 Hepatitis C virus infection

453 Worldwide, 177.5 million adults are infected with hepatitis C virus, especially in Asia and Africa 454 [89]. In Europe, estimates of HCV prevalence is generally around 1% and up to 7% among 455 migrants [58] . Studies form Italy and the Greek-Turkish border show 0.8% and 3.7%, 456 respectively of migrants were HCV antibody positive; however, age-disaggregated data was 457 not provided in those studies [20; 33]. Most HCV-infected children and adolescents are 458 asymptomatic, with normal liver function tests. Transmission in children is mostly from 459 mother to child, with 80% of those infected becoming chronic [125]. Spontaneous resolution 460 of perinatally acquired HCV is rare after the age of 3 years. Like HBV, the goal of screening 461 migrant children is to prevent progression to decompensated liver disease and hepatocellular 462 carcinoma. However, as data on HCV infection in migrant children is scarce a general screening 463 remains controversial. If screening is performed serology should be used as generally most children older than 15-18 months with chronic HCV-infection are seropositive. In anti-HCV 464 465 antibody positive patients, chronic infection is diagnosed by polymerase chain reaction for 466 HCV RNA. In infants below 18 months of age, anti-HCV antibodies can still be of maternal 467 origin; therefore, in this age group HCV RNA testing is required or testing is deferred to after 468 18 months of age.

469

#### 470 Tuberculosis

Recommendation 10: Perform a tuberculosis\* screening (tuberculin skin test/ interferon-gamma release assays) followed by chest x-ray if either test is positive in:
a) all migrant children < 5 years of age (Grade D)</li>
b) migrant children from a high-endemic country including but not limited to sub-Saharan-African region, Afghanistan, Somalia/Eritrea (Grade C)

Note: in case of clinical suspicion of active tuberculosis (prolonged fever, poor weight gain or weight loss without another explanation) perform all investigations according to national recommendations (Grade B)

471 In recent years, TB notification rates have decreased in most EU/EEA countries, and 472 tuberculosis now predominantly affects vulnerable populations including migrant children. 473 Between 2000 and 2009, 15% of paediatric tuberculosis cases in Europe were of foreign origin 474 [98]. Many migrants originate from countries with a high incidence of tuberculosis. Having 475 lived in crowded conditions during their travel further increases the likelihood of recent 476 exposure to tuberculosis [83]. The incidence of tuberculosis in migrant children has been 477 reported to be higher compared with non-migrant children in several European countries [70; 478 99]. Children compared to adults are more likely to progress from tuberculosis infection to 479 disease and develop more severe forms of disease [114]. However, they have excellent 480 outcomes if diagnosed and treated early [68]. Dedicated policies for tuberculosis screening in 481 migrants have a long tradition in many countries but mainly target adult patients [105; 115]. 482 In Greece, latent tuberculosis infection has been detected in 2.7% of migrant children [106]. 483 Further studies in Germany, the United States of America, Australia and New Zealand show a 484 higher prevalence of latent tuberculosis infection of 15% to 24% [40; 72; 118; 147]. The highest 485 rates of latent tuberculosis infection of 60% were found in a study in Spain among adolescent 486 and young adult immigrants from sub-Saharan Africa [124]. Active tuberculosis is however 487 rarely identified in routine screening of migrants [72]. The sensitivity of the tuberculin skin 488 test and interferon gamma release assays to detect active tuberculosis is estimated to be 70-489 90% [77]. The specificity for interferon gamma release assays is above 95%, but the tuberculin 490 skin test cross reacts in patients immunised with bacille Calmette-Guerin (BCG) vaccine or in 491 those infected with non-tuberculous mycobacteria and its specificity is therefore lower [103]. In patients vaccinated with BCG an interferon gamma release assays may be used instead of a tuberculin skin test, although interferon gamma release assays may be false negative in young children due to lower interferon gamma expression in younger individuals [129]. Several studies have analysed cost-effectiveness for latent tuberculosis in children and adults with the majority showing that screening is cost-effective particularly in young individuals from countries with high tuberculosis incidence [34; 148].

498

# Recommendation 11: Schedule a follow-up appointment to complete the catch-up immunisations, screen for mental health risk factors and symptoms\*, female genital mutilation\* and coordinate any ongoing care needs the child may have.

499 Continuity of care is important and careful consideration should be put into the scheduling of 500 follow-up appointments. These should be used to review results and continue catch-up 501 immunisations. Mental health concerns including emotional and behavioural problems in 502 migrant children and adolescents are best approached in follow-up appointments unless 503 these are identified as the main health need by the families or children in the initial 504 appointment. Unaccompanied migrant children and adolescents are an important risk group 505 for mental health problems [84], which is associated with the stress of separation from 506 parents, traumatic events including the risk of sexual and gender-based violence and the lack 507 of social support [5]. Signs of mental distress in migrant children and adolescents are very 508 diverse and depend on age, traumatic experiences and social background and may be 509 challenging to detect [6]. Very few screening instruments have been tested for diagnostic 510 accuracy in migrants in general. The strengths and difficulties tool (http://www.sdqinfo.com/), 511 which is available in over 60 languages, can assist in the identification of symptoms. For further 512 information on screening tools and approaches we also refer to a recent review on this topic 513 [59]. Most of the children and adolescents will not require treatment as symptoms fade over 514 time in the host country. Referral to child psychiatrist however should be considered when 515 there is significant impairment of daily activities and/or ineffective or harmful coping 516 strategies in the child or family [84].

517

518 Female genital mutilation (FGM) may be another topic to be discussed in follow-up 519 appointments. FGM consists of procedures that intentionally alter or cause injury to the 520 female genital organs for non-medical reasons involving partial or total removal of the 521 external female genitalia [144]. Worldwide, at least 200 million girls and women have 522 undergone FGM [144]. The practice is highly concentrated in countries from the Atlantic Coast 523 to the Horn of Africa, in areas of the Middle East (such as Iraq and Yemen) and in some 524 countries in Asia (like Indonesia), but it exists also in other regions of the world [132]. In 525 Europe, more than half a million first-generation migrant girls aged 10 years and older and 526 women have undergone FGM for cultural or non-therapeutic reasons, most probably prior to 527 arrival in Europe [137]. FGM can have serious and long-lasting consequences including 528 genitourinary problems an increased risk of childbirth complications [7; 62], and significant 529 psychological sequelae [139]. Signs of FGM noted during the examination (it may be 530 appropriate to only let female doctors perform genital examinations in female migrant 531 children) should lead to referral to a physician experienced in the management of girls and 532 women with FGM [144].

533

534 Based on this first health assessment, immediate treatment should be provided and referral

Recommendation 12: Provide the caregiver with a document of the health assessment and interventions and store a copy of this in your records or, if available and compliant with data protection law of your country, in any encrypted digital form enabling both migrants and healthcare institutions to have fast and secure access.

535 to specialist care should be initiated if needed. Documentation of history, investigations and 536 treatment is important to provide optimal and timely care and to avoid unnecessary 537 investigations. A copy of the health record should be provided to the child's caregiver at the 538 end of the assessment. This is particularly important, as it will help future providers, if the 539 child moves onward or is seen by a provider at a facility that does not have access to the 540 records from the visit. It may also help to ask the parent or child to take a picture of their most 541 important health information such as a vaccination chart to minimise the risk loss of 542 information.

543

544 A summary of all recommendations can be found in **Table 3**.

- 545
- 546 Limitations

547 This recommendation is based on currently available limited data on migrant health in 548 children. As migrant patterns will change and new evidence will become available some of the 549 specific recommendations will inevitable require adaptation.

550

#### 551 Conclusion

The current document provides a recommendation based on expert opinion and available evidence for a standard of medical care for migrant children. These include general topics on ethical standards, use of interpreters, specific recommendations for prevention or early detection of communicable and non-communicable diseases and practical advice on followup consultations and documentation. It is fundamental that migrant children in Europe are treated according to United Nations Convention on the Rights of the Child to ensure that the receive a comprehensive, patient-centred health care.

560	Acknowledgments:
561	The author would like to thank Ayesha Kadir and Anders Hjern for helpful comments on the
562	manuscript. We would like to thank René-Marie Meignan for designing the icons.
563	
564 565	Compliance with Ethical Statements
566	Conflict of Interest: The authors declare that they have no conflict of interest.
567	Funding: There is no funding source.
568	Ethical approval: This article does not contain any studies with human participants or
569	animals performed by any of the authors.
570 571 572	Author contribution
573	LS, CW, SdT and NR conceived the manuscript. LS and NR performed the data acquisition and
574	wrote the first draft of the manuscript. TS, UvB and JB critically and substantially revised the
575	draft of the manuscript. All authors approved the final manuscript.
576 577	
578 579	what is known" and explain "what is New"
580 581	Not applicable
582	

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<b>Fable 2:</b> Conditions with recommendations in nationa	I clinical guidelines for	child migrant care in Europ	e and selected non-European countries.
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Country	DE	СН	AU	UK	SP	FI	IT	NL	CA	US	AUS
[Reference]	[107]	[8; 38]	[43]	[130]	[85]	[96]	[97]	[39]	[109]		
Vaccine-preventable in	nfection										
Measles, mumps, rubella	Complete	Complete	Complete	Complete	Complete	Complete	Complete	Complete	Complete	Complete	Complete
Diphteria, pertussis, tetanus, polio	Complete	Complete	Complete	Complete	Complete	Complete	Complete	Complete	Complete	Complete	Complete
Varicella infection		Complete >11 y	Complete, recommend ed			Complete			Complete <13 y; screen >13 y		Complete <14 y; screen ≥ 14 y
Haemophilis influenza b infection	Complete	Complete <6				Complete	Complete	Complete			Complete < 5 y
Influenza			Complete, recommend ed								
Meningococcus B or C infection	Complete	Complete, recommen ded	Complete, recommend ed		Complete	Complete	Complete	Complete			Complete
Pneumococcus infection	Complete	Complete, <5 y, recommen ded	Complete			Complete	Complete	Complete			Complete, < 5 y
Hepatitis A infection	If increase in transaminase		Screen, all		Screen					Be alert	
Hepatits B infection	Complete	Screen, all	Screen, all	Be alert Screen, consider	Screen, all	Screen, all	Screen, all	Complete	Screen, at risk	Screen if no document ation, all	Screen, all
Hepatitis C infection	If increase in transaminase		Screen, all	Screen, consider	Screen, all		Screen, all	Be alert	Screen, at risk	Be alert	Screen, at risk
Hepatitis D infections										Be alert	
Tick-born encephalitis			Complete, recommend ed								
Yellow fever											Pre- immigration: if relevant
Polio											Pre- immigration: if relevant
Rotavirus	Complete										
Other infections											

Country	DE	СН	AU	UK	SP	FI	IT	NL	CA	US	AUS
[Reference]	[107]	[8; 38]	[43]	[130]	[85]	[96]	[97]	[39]	[109]		
Malaria		Screen, at risk	Screen, at risk	Screen, consider, at risk	Screen, at risk		Screen, at risk	Be alert	Screen, at risk	Treat or screen, at risk	Screen, at risk
Tuberculosis	Screen, all	Screen, all < 5 y; at risk >5 yr	Screen, ≥ 6 y Be alert, all	Be alert Screen, at risk	Screen, all	Screen if not vaccinated	Screen, all	Screen, at border	Screen, at risk	Screen, all	Screen, all
HIV	Screen if symptoms	Screen, all	Screen, all	Be alert Screen, consider	Screen, at risk	Screen	Screen, all	Be alert	Screen, at risk	Screen if no document ation, all	Screen ≥ 15 y, or younger and at risk
Schistosomiasis infection	Screen if symptoms	Screen, at risk	Be alert	Screen, consider, at risk	Screen, at risk		Screen if negative stool probe and eosinophili a		Screen, at risk	Screen or treat, at risk	Screen, at risk
Helminth (incl strongyloides)	Screen if symptoms	Screen, at risk	Be alert	Screen or treat	Screen, all	Screen, at risk	Screen, all		Screen, at risk	Be alert- screen	Treat
Protozoan infection	Screen if symptoms	Screen or treat, all	Be alert		Screen, all	Screen, at risk	Screen, all			Be alert	Screen, all
Chagas		Screen, at risk	Be alert		Screen, at risk					Be alert, at risk	
Leishmaniasis	Screen if symptoms	Be alert	Be alert	Screen, consider, at risk	Be alert					Be alert, at risk	
Leprosy					Be alert						
Typhoid fever	Screen if symptoms	Be alert								Be alert, if febrile	
Dengue Infectious skin disorder like scabies, dermatological mycosis, impetigo, lice, infected eczema	Screen if symptoms	Be alert Be alert	Be alert	Be alert	Be alert					Be alert	Screen, all
Syphilis		Screen <2 y; screen other ages if at risk	Screen <2 y			Screen	Screen, all			Screen if no document ation, all	Screen, at risk
Other STI					Screen, at risk					Be alert, at risk	Screen, at risk
Helicobacter pylori infection										Be alert	Screen, at risk
Mental health and phys	sical/emotiona	I maltreatm	ent								

Country	DE	СН	AU	UK	SP	FI	IT	NL	CA	US	AUS
[Reference]	[107]	[8; 38]	[43]	[130]	[85]	[96]	[97]	[39]	[109]		
PTSS	Be alert	Be alert	Be alert	Be alert	Be alert			Screen	Be alert	Be alert	Pre- immigration: Screen, all
Child maltreatment			Be alert	Be alert				Be alert	Be alert		
Sleep and behavorial disturbances				Screen	Be alert			Screen		Be alert	
Social support and education		Evaluate		Evaluate	Evaluate and inform			Evaluate			
Functional symptoms		Be alert									
Chronic and noncomm	unicable dise	ases	T	T	I		1	r	1	1	
	_	_	_	_	_			_			
Anemia	Be alert	Be akert	Be alert	Be alert	Be alert		Be alert	Be alert		Be alert	Screen, all
Iron-deficiency anemia	Screen, suggested	Screen, all	Be alert		Screen, all Treat, at risk		Screen	Screen if clinical suspicion	Screen, at risk	Screen, at risk	Screen, all
Hemoglobinopathy		Consider, at risk	Be alert		Screen, at risk			Screen if clinical suspicion		Screen, at risk	
Thalassemia					Screen, at risk						
G6PD deficiency			Be alert				Screen, if anemia and at risk			Screen, at risk	
Nutritional deficiencies		Be alert	Screen 25/OHD, consider Treat (vit D), all	Be alert	Be alert Screen 25/OH/colec alciferol, at risk Treat (vit D), at risk		Be alert Screen electrolyte s			Be alert	Screen vit D, at risk Screen vit B12, at risk
Lead poisoning					Screen, at risk and with symptoms					Be alert Screen, at risk	
Liver or kidney failure			Screen, all				Screen, all				
Hypertension										Screen if 3yrs or older or at risk	
Congenital metabolic or endocrine disorders			Be alert Screen TSH		Screen, if not done previously		Screen TSH and glucose	Neonatal screening if < 6 months of age		Be alert, at risk	

Country	DE	СН	AU	UK	SP	FI	IT	NL	CA	US	AUS
[Reference]	[107]	[8; 38]	[43]	[130]	[85]	[96]	[97]	[39]	[109]		
Congenital defects or genetic conditions							Be alert	Evaluate		Be alert, at risk	
Dental disease	Screen	Screen, all	Screen, all	Check			Screen, all		Screen, all	Screen, all	Screen, all
Vision impairment	Screen, suggested	Screen, all	Screen, all	Screen if concerns			Screen, all	Screen, all	Screen, all	Screen, 3 yrs and older	Screen, all
Hearing impairment	Screen, suggested	Screen, all	Screen if concerns	Screen if concerns			Screen, all	Screen, newborns		Screen, newborn and 4 yrs and older	Screen, all
Growth and development impairment	Screen	Screen, all		Screen, all	Screen, all		Screen, all	Screen, all		Screen, all	Screen, all
Women's health											
Contraception issues				Screen, adolescents				Evaluate and inform	Screen, adolescents	Screen, adolescent s	Inform adolescents
Human papillomavirus infection	Vaccinate female 9-14 y	Vaccinate, female 11- 14 y	Vaccinate, all					Vaccinate, girls ≥ 12 y	Vaccinate ≥ 9 y		Vaccinate, adolescents
Cervical abnormalities									Screen, adolescents		Standard prevention screening
Sexual health (for example. sexual exploitation, female genital mutulation)	Check FGM	Evaluate		Evaluate and inform	Evaluate and inform			Evaluate and inform		Evaluate and inform	Be aware
Lifestyle-related problems											
Alcohol, tobacco or drug abuse		Be alert		Inform, adolescents				Inform			
Obesity or malnutrition		Be alert		Inform, adolescents	Inform			Inform		Be alert	

Complete\*: complete vaccination schedule; be alert: look for signs and symptoms; screen\*\*: screen; evaluate: discuss; consider: consider if; at risk: only in children at risk (if endemic in country of origin, if exposure, if certain age group).\* If guidance document specifically included that action was recommended, this is was added to the table. \*\* if guidance specifically addressed that all or only children at risk should be screened, this information was added to the table. Link to complete database on EAP website. **Table 3: HEALTH-** Acronym, summarizing key questions for practitioners providing health

 care to asylum-seeking patients

Category	Questions				
H ome	Country of birth and/or country of origin?				
	Did (s)he receive health care (incl. screening/prevention)				
	before leaving home?				
E scape	Escape route? Total duration of Escape?				
A rrival	Date of arrival in host country?				
L anguage	Languages spoken?				
	Preferred language including dialect?				
	Need of an interpreter?				
	Preference male/ female interpreter?				
T ransition countries	Did the (s)he stop for a longer time in another country?				
	Did (s)he become ill in a transition country?				
	Did (s)he receive health care (incl. screening/prevention)?				
H ost country	Did the (s)het become ill in the host country?				
	Did (s)he receive health care (incl. screening/prevention)?				
	Does (s)he have an allocated primary care physician?				

#### Table 3: Summary of the recommendations



Check if the migrant child is accompanied by at least one parent or a responsible caregiver.

Check if the parent/carer is capable to communicate sufficiently; access professional interpreter services if limited language proficiency is suspected.

Ask about health problems that the parents and the children themselves identify.

Ask about growth and development and perform a physical evaluation including of weight-for-age and height-for-age, development and vital parameters. Be alert for signs of congenital anomalies (i.e. heart defects), non-communicable (developmental delay and tumours) and infectious diseases (hepatosplenomegaly and lymphadenopathy).

Ask for vision and hearing problems; perform a routine vision and hearing screen.

Examine the entire skin and oral cavity and be alert for signs of anaemia, scabies, impetigo, malnutrition, tooth decay and scars.

Check immunisation status and - if unknown or incomplete - start catch-up immunisations according to national recommendations as soon as possible.

Treat empirically for intestinal parasites with albendazole.

Take a blood sample to measure

- a) haemoglobin to check for anaemia and treat iron deficiency if present
- b) HBV-antibodies (Hbs-Ag, anti-Hbs and anti-HBc)

ADD

- c) if risk factors or signs for nutritional rickets:
- d) if from sub-Saharan Africa:
- e) if from sub-Saharan Africa or known risk:
- f) if febrile:
- g) if immunosuppression known or forseen:
- h) if sexually active or abused:

#### OPTIONAL

i) HCV-antibodies

#### Vitamin D Schistosomiasis\* serology and CCA urine test

HIV serology or PCR Malaria screen

Strongyloides serology Syphilis serology

Perform a tuberculosis screening (tuberculin skin test/ interferongamma release assays) followed by chest x-ray if either test is positive in:

a) all migrant children < 5 years of age

b) migrant children from a high-endemic country including but not limited to sub-Saharan-African region, Afghanistan, Somalia/Eritrea



10

Schedule a follow-up appointment to complete the catch-up immunisations, screen for mental health risk factors and symptoms, female genital mutilation and coordinate any ongoing care needs the child may have.



Provide the caregiver with a document of the health assessment and interventions and store a copy of this in your records or, if available and compliant with data protection law of your country, in any encrypted digital form enabling both migrants and healthcare institutions to have fast and secure access.

#### **Supplementary Material**

Level	Treatment / Prevention	Prognosis	Diagnosis	Symptom prevalence
1	RCT or SR from RCT	Validated CDR	Validated CDR	Prospective cohort study
2	Cohort study	Retrospective cohort study; CDR validated only on split samples	Exploratory cohort study; CDR validated only on split samples	Retrospective cohort study
3	Case-control study		Non-consecutive study; or without consistently applied reference standards	Non-consecutive cohort study, or very limited population
4	Case-series	Case-series	Case-control study	Case-series
5	Expert opinion	Expert opinion	Expert opinion	Expert opinion

Table 1 & 2 . Quality of evidence and grades of recommendation (adapted from [87])

CDR: clinical decision rule; RCT: randomised controlled trial; SR: systematic review

Level	Evidence
A	Consistent level 1 studies
В	Consistent level 2 studies
С	Consistent with level 3 and 4 studies
D	Level 5