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Are refugees arriving in Denmark an under-immunised group for measles?

A cross-sectional serology study

Abstract

Background

In 2018, Europe faced the highest number of Measles cases in a decade. In Denmark, the childhood vaccination programme has a coverage of approximately 90%. To eliminate the disease, vaccine coverage needs to be above the herd immunity threshold of 95%. This can be even more difficult to obtain, when vaccination programmes break down due to war, natural disasters etc. and concern has been raised, that unvaccinated refugees could facilitate spread of measles when migrating.

Methods

In order to address this concern, we tested 513 newly arrived refugees and family reunified refugees aged between 0 and 70 years for measles IgG antibodies. The participants were tested as part of a general health assessment between May 2016 and October 2018. In the cohort, 50% were males and the majority came from Syria (55%).

Results

We found that 85% of the total group of refugees had immunity against measles. The 15% lacking antibodies, were evenly distributed between the various countries of origin. Moreover, we found immunity to increase with age, leaving young children most vulnerable to infection, 79.9% (<19 years) vs 89.1% (>=19 years).

Interview questions on previous vaccinations did not correlate to serology.
Conclusion

Refugees have measles immunity slightly lower than the host population.

Introduction

In 2018, Europe faced the highest number of measles cases in a decade [1]. Measles is a severe and highly communicable disease caused by the morbilli virus. Although a safe and efficient vaccine is available, the virus causes approximately 110,000 deaths per year worldwide – predominantly children under the age of five years. [2,3] Typical symptoms include high fever, cough, coryza, conjunctivitis and maculopapular rash.

Measles may lead to serious complications including encephalitis and death [4]. The key strategy for elimination is to achieve and sustain herd immunity ≥95% [5], but many European countries have still not been able to reach this level of immunity[6]. E.g. in Denmark, 93% of children receive the first vaccination against measles, but only 87% receive the second dose, leaving part of the population susceptible to measles infection[7].

Migrants often come to Europe from countries, where health systems and vaccination programmes have collapsed [8]. Also, only a minority of refugees have access to routine vaccination and regular health care services. In 2016, the vaccination coverage for first measles vaccine was 79% in Syria, 75% in Afghanistan and 45% in Somalia and second dose coverage was 69% in Syria and 51% in Afghanistan (data were not available for Somalia)[9]. At the same time, refugees face overcrowding, malnutrition, mental and physical stress and poor sanitation, thus increasing susceptibility to infections [10]. This has been considered a risk factor in reintroduction of measles in Northern Europe, where outbreaks have been reported to involve refugees [11,12]. Although the health needs of refugees may be similar, the health assessments being offered differ widely in the receiving countries[13] and implementation of effective vaccination programmes for refugees in Europe is challenging[14]. As a consequence of this, Mipatrini et al. found that
foreign born children had up to three fold higher risk of being unvaccinated compared to European born children [14]. Initiatives to improve vaccination coverage has included targeting migrants for catch-up vaccination. A recent review by Hui et al found intervention studies showing a small but promising effect on vaccine uptake with social community outreach /mobilisation, education campaigns and planned vaccination programmes[15]. Another important stepping stone in the elimination of measles, is also improving uptake for the second dose of vaccination, as coverage is significantly lower than first dose uptake in most countries[9] and has been suggested as an explanation to the persistence of measles in Europe [16] (One dose is of MMR vaccine is approximately 93% effective at preventing measles and two doses approximately 97% effective[17]). Data on vaccination status of migrants entering Europe is scarce. In Denmark, asylum seeker children ought to receive vaccines according to the Danish national immunisation programme. However, studies have shown refugee children to have a lower uptake of all immunisations in the programme compared to Danish born children, with the lowest uptake of immunisation against diphtheria, tetanus, pertussis and polio (HR=0.50; (95%CI:0.48–0.51))[18]. In addition, adult asylum seekers do not routinely receive an evaluation of vaccination status. Recent surveys from other European countries have found that measles immunity among adult asylum seekers was relatively high with seroprevalences ranging between 73 and 92.6%, although not sufficient to reach herd immunity,[19–25]. Only one of these studies involved seroprevalence results from Scandinavia and this study included adults only[25]. None of the studies included family reunified refugees. As the demographic constitution of the refugee population is continuously changing, ongoing studies are needed to follow the development in measles immunity status in refugees.

To address this, we conducted a study to examine the prevalence of protective antibodies against measles in newly arrived children and adult refugees in Northern Europe to assess 1) the degree of immunity and 2) risk factors for sero-negativity including country of origin, gender and age.

Materials and methods
We performed a cross-sectional study on morbilli serostatus in a cohort of newly arrived refugees in Denmark. The study was conducted in Aarhus, the second largest city in Denmark. The municipality of Aarhus receives refugees through Danish asylum centres and the UNHCR – in this paper referred to as “regular refugees” - and family reunified to refugees. Both regular refugees and family reunified refugees are offered a voluntary health assessment after receiving residence permit in Aarhus. The health assessment is conducted by a physician assisted by an interpreter. It includes a medical interview, a physical examination and a panel of blood samples. Nearly 90% (695/796) accept to undergo this health assessment (Table 1).

Serostatus was evaluated testing serum levels of IgG and IgM against morbilli virus using chemiluminescence immunoassay (CLIA) performed on LIAISON®XL (Liaison XL analyser, Diasorin, Italy) according to manufacturer’s recommendations at Department of Clinical Microbiology, Aarhus University Hospitals diagnostic laboratory. Threshold values of IgM regarded as positive are ≥1.1 (cut-off index; i.e. the values have no unit of measurement), inconclusive 0.9 ≤ x < 1.1 and negative <0.9. Level of IgG regarded as protective is ≥16.5 AU/mL (arbitrary units per mL), inconclusive 13.5 AU/mL ≤ x < 16.5 AU/mL and non-immune; < 13.5 AU/mL.

Based on the serological status, all non-immune participants were referred to their general practitioner for catch-up immunisations. When a participant needed help reaching their general practitioner, we cooperated with the participant’s assigned social worker, ensuring linkage to care.

A database was created using the RedCAP (Vanderbilt, United States of America) system, where data on country of origin, age, gender and blood sample results were stored. For the age analysis, the participants were divided into age groups age <5, ≥5>10 years, ≥10<19 years, ≥19<30 years, ≥30 <45 years and ≥45 years. WHO classification of macro-geographical (continental) regions was used in the analysis (EMRO=Eastern Mediterranean Region, ARFO=African Region and EURO = European Region) [26]. We performed a bivariate analysis to establish the prevalence of morbilli immunity based on country of origin, age and gender using Persons Chi-square tests. The statistical analysis was completed using Stata (StataIC
version 15 for mac). P-values below 0.05 were considered statistically significant. Polytomous outcomes were dichotomized for interpretability of model results. To account for various distributions of nationality, all results are stratified by nation.

The Danish Data Handling Authority (file number 2015-55-0586) and the Danish Patient Safety Authority authorized this project (file number 3-3013-2624/1). The Central Denmark Region Committee on Health Research Ethics assessed the project and concluded approval was not required.

Results

Between 2016 and 2018 the municipality of Aarhus received 445 regular refugees and 351 family reunified refugees. (Table 1)

(Table 1: Number of arrived refugees and coverage of health assessments in Aarhus from 2016 to 2018.)

Morbilli antibody screening was included in the health assessment in May 2016 and was still part of the blood sample panel when the study period ended 31st of October 2018. A flow chart of study participants is presented in Figure 1.

(Figure 1: Flow chart of participants.

Of the 796 regular refugees and family reunified arriving between 2016 and 2018, a total of 695 participated in a general health assessment at Aarhus Municipality. During the study period from May 2016 to October 2018, where morbilli antibody detection was included in the blood sample panel, 513 regular and family reunified refugees participated.)

Of the 513 participants, 258 were females (50.3%) and 255 were males (49.7%) between five months and 70 years of age (median age 21.8). They originated from Syria, Iran, Iraq, Afghanistan, Pakistan, Eretria,
Ethiopia, Somalia, Lebanon, Pakistan, Russia, Palestine, Morocco and Jordan. More than half of the population came from Syria. In total, 47% were <19 years old (6% (n=30) were <5 years of age, 41% (n=209) were ≥5 to <19 years of age) and 13.8% (n=71) were ≥45 years. Demographics are shown in Table 2.

(Table 2: Demographics and the degree of immunity to measles for the study population. Countries of origin are shown separately and by WHO regions. Sero-protection was analysed using chi2 test for each country and region separately. ** Only positive results included, no inconclusive.)

The prevalence of morbilli virus IgG in all tested refugees was 84.8% (n=435) while 13.3 % (n=68) were below the defined positive cut off. The remaining 2.0 % (n=10) were inconclusive and were regarded non-immune. None of the participants had IgM antibodies against measles; indicating that none of the participants had an active measles infection at the time of screening.

Country-specific seroprevalence was compared to the herd immunity threshold of 95% for all countries with ≥ 5 participants. Only one country, Somalia, had seroprevalence above 95%. Among the 30 Somalian participants we found 100% were immune, probably due to childhood infection rather than immunisations.

The highest percentage of the non-immune was found in individuals from Eretria (n = (34/44) 77.3%). Using a chi2 test, we found no significant association between origin (countries/regions with ≥ 5 participants) and immunity status neither in relation to country of origin nor to region of origin. Seroprevalence and results are depicted in Table 2 and Figure 2.

(Figure 2: Age groups by region of origin as n (columns) and immunity as % of population (line))

We found lacking immunity in all age groups <45 years as shown in Table 3. The lowest degree of immunity was seen in the youngest age group (<5 years); 63% (19/30) (p=0.001) and adolescents/young adults (≥10 years)
to <19 years/≥19 to <30 years); 81% (106/131) /82% (86/105) (non-significant p=0.152/0.355). The highest degree of immunity was in the oldest age group (≥45) of 100% (71/71) (p=<0.000) indicating the overall degree of immunity to increase with age as also illustrated in Figure 2. A total of 277 refugees arrived as regular refugees (162/58% male) and 236 as family reunified refugees (92/39% male). When comparing if refugees had arrived as regular or family reunified refugees, we found no difference regarding the degree of measles immunity. (Immunity in regular refugees (n=241) p=0.141/ family reunified refugees (n=194) p=0.131). Additionally, we did not find a correlation between gender and measles immunity (data not shown).

(Table 3: Total number of newly arrived refugees (total n), measles sero-protection level (n)/ % by age groups in years. Sero-protection was analysed for each age group separately using a chi2 test.)

Of the 513 participants, 498 attended the medical interview in the health assessment. Within this group, 75.5% responded they had followed a childhood immunisation programme in their home country. Surprisingly, in the subgroup of non-immune(n=64) attending the interview, 66% (42/64) responded they had followed an immunisation programme. Using a chi2 test we did not find any correlation between having immunity and replying having participated in a childhood vaccination programme (p=0.154). Furthermore, in the subgroup of immune (n= 424) seven participantes responded they had not followed a vaccination programme and 27 did not recall having had any previous vaccinations.

The medical interview included questions on education level for adults (≥19). Of the 274 adults participating, data on educational level were available for 268. We found no correlation between length of education and immunity status. (Never attended school p =0.074, < 3 years of schooling p= 0.217, 3-5 years of schooling p = 0.165, 6-8 years of schooling p=0.242, 9-10 years of schooling p= 0.161, completed high
school p= 0.052, further academic education 2-3 years p=0.435, further academic education 4-6 years p= 0.959) and further academic education >6 years (PhD) p=0.272)

Discussion

Our data show immunity against measles for newly arrived refugees in Denmark in 85% of the study population. Seroprevalence was below the herd immunity threshold of 95% in most countries in the study. The largest proportion of refugees in this cohort were minors and refugees originating from Syria. We found that age under five years was associated with lacking immunity; neither country of origin nor gender was significantly associated with lower immunity against measles (except for Somalia).

Finding a representative cohort for the refugee population in Northern Europe is challenging, as the countries of origin of refugees vary due to political, economic, cultural and historical reasons. This could create bias. However, as the total Danish refugee population generally correlates with the European refugee population, we expect this cohort to be generalisable for refugee populations in many other recipient countries. E.g. some of the largest groups of asylum seekers from non-EU countries in Europe and Denmark are similar (Syria, Afghanistan and Iraq).[27,28] To our knowledge, this is also the first study on measles immunity in refugees, with a known denominator as all refugees coming to Aarhus are part of the population the study population is sampled from.

We obtained a high participation rate by including the screening as part of a general migrant health assessment involving both psychical, mental and social health issues. Both refugees, social workers and health workers stated the examination was very meaningful for the transition and the high participation rate may be attributed to this. The study did not include specific questions on this matter.

Our findings on immunity are in line with those reported in recent similar serology studies from Northern Europe, where measles immunity was reported between 79.9 and 92.6% [19–22,25]. The study population in these studies were also primarily from EMRO.
In correspondence with our results, several other studies also found low immunity in young adults, although age groups were not directly comparable [19,20,24]. This may be partly explained by the lower levels and faster waning of vaccine-induced antibodies compared to antibodies produced after natural infection [29].

Two studies from Central Europe with different refugee populations found lower immunity; a study on Eritrean refugees in Switzerland found 76.2% to be immune[23] and a study from Luxembourg from 2012 primarily involving refugees from Balkan found 73% to be immune[24] The low immunity in refugees from Balkan was also found in a study from Sweden, where only 68 % of immigrants/refugees from the former Yugoslavia and Albania were immune. [25]. The various differences are most likely due to geographical and demographic changes in the arriving refugee population as well as vaccination coverage and outbreaks in the migrants’ home countries. Our study did not include participants from the Balkan countries, but we found 2/4 participants from Russia to lack immunity. In the recent pan-European measles epidemic a key group involved were eastern European migrants and the five countries from the WHO Europe Region still having endemic transmission (Bosnia and Herzegovia, Russia, Serbia and Ukraine) are all situated in the eastern part of the region[30]. During the outbreaks in Europe in 2019, the highest number of cases were found in Ukraine with 56,802 cases[31]. The Balkan and Eastern European migrants are often left out in health policies of newly arriving migrants. Attention to these groups, both scientifically and in health systems, could be important in the elimination of measles in Europe.

When looking at ethnicity instead of country of origin, we found no difference in immunity regarding Palestinian ethnicity, but we found participants with Kurdish origin to have significantly higher immunity (p=0.022) In most available recent studies on measles immunity in refugees in Northern Europe, study populations have consisted of asylum seekers and a high proportion of male participants (75.6-81 %) [19–23]. This is likely due to the custom of male refugees travelling in advance and females and children arriving later as family reunified. Our study has been conducted after refugees received their residence permit and has included family reunified refugees showing a more accurate picture of the potential disease burden in
the society. The gender distribution of 50:50 in our study might be attributed to this fact, as the same
tendency was seen by Hübchen et al who included both asylum seekers and refugees in a cohort with 57%
males[24].

The concerningly high proportion of 35% non-immune children <5 years suggests that current screening in
asylum centres may not function adequately and demonstrates that there is a need for ensuring a
systematic health assessment in resettling refugees. One of the non-immune children in this study had
been through seven different asylum centres. A study by Nakken et al found that health care providers in
Danish asylum centres adopt various tactics to ascertain the immunisation needs in children. They found a
need for clear national guidelines to determine vaccination needs of asylum seeking children and
encouraged international efforts to secure reliable immunisation documentation[32].

Jablonska et al[20] found total immunity to be higher than demonstrated in our data (89.9%) using the same
laboratory analyses, but with positive results defined as >13.4 AU/ml. We regarded an IgG level of 13.5 ≤
AU/ml x < 16.5 AU/ml to be inconclusive and ≥16.5 AU/ml to be considered with immunity. When adding
our inconclusive results to the immune, the percentage rises to 86.7 and thus very similar to the findings of
Jablonska et al.

As mentioned in other studies [20,21,23,24], studies on measles immunity are all based on humoral
immunity (antibodies). However, also cellular immunity contributes to the immunity implying that the
protection against measles could be underestimated. Nevertheless, the analysis of serostatus is currently
the only feasible method of assessing protection, as vaccine documentation and patient memory of
immunisations has also proven unreliable in other studies of refugees and vaccine preventable
diseases.[33,34]
Surprisingly, we did not find correlation between the interview questions on previous vaccinations and serology. Part of the discrepancy between not recalling immunisations and having immunity would be attributable to immunity after natural infection with measles or individuals had received the vaccine but had not seroconverted due to loss of potency in transit or reconstitution[35]. However, this cannot explain the high percentage of participants responding they had followed an immunisation programmes but had no antibodies. This is more likely due to recall bias.

Ensuring vaccination to refugees in Europe is currently addressed by several pan-European institutions. In 2018, the ECDC published guidelines on vaccination of newly arrived refugees including recommendations concerning vaccination against measles/mumps/rubella (MMR) to all migrants without immunisation records. The ECDC guideline also highlights that various migrant populations are vulnerable to infectious diseases and have low levels of vaccination coverage as well as facing barriers to accessing health care after arrival to the EU/EEA. [36] These concerns are shared by The European Vaccine Action Plan 2015-2018(EVAP) from WHO Europe stating vaccination as a right and that priority is not being given to ensure this right for migrant populations. [37] All 53 member states of WHO Europe, have endorsed the EVAP strategy to eliminate Measles and Rubella[38]. Another publication by WHO, also highlights the importance of ensuring immunisation services for migrants and refugees, as well as finding effective mechanisms to counteract barriers in access to vaccination services.[39]

Furthermore, a recent cross-sectional survey of measles vaccination policies on recently arrived migrants in EU/EEA countries found that this type of policy was only available in six of 32 participating countries and in these six countries the guidelines were not consistently implemented.[40] Both the EVAP, the ECDC guideline and WHO mention the lack of data and the quality data as important obstacles in linkage to care and treatment for migrants with infectious diseases.[37,39,41]

The current study also has several limitations. Firstly, only 87.3% of the refugees participated in the health assessment and the remaining 12.7% may be distributed differently. It could be argued that refugees
attending the assessment might be showing “health seeking behaviour”. Still, with the high participation rate, we find that the cohort can help answer the questions of measles immunity in newly arrived refugees. Secondly the subgroup analysis was conducted on relatively small groups resulting in less accurate estimates. Nevertheless, even though our cohort only represents a small sample of the refugee population in Denmark, the observed non-immunity rate of 15% is concerning.

Conclusion

In summary, we found that newly arrived refugees have a relatively high prevalence of morbilli virus IgG, although there is still a gap before reaching the herd immunity threshold. We found little correlation between sero-status and self-reported vaccine coverage, emphasising that self-reporting of vaccine reception is unreliable. We identified children under five years to be overrepresented in the non-immune cohort. As non-immune were seen from most countries and in most age groups targeting only specific subgroups will not be a feasible approach. We recommend that vaccination (with two doses for children and one for adults in accordance with ECDC guidelines[36]) is offered as part of a general health assessment, to refugees who are not able to document immunisations from their country of origin or from a refugee camp, in order to help stop the spread of measles in Europe.

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