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Original Article

Effect of immigration on mortality trends in sickle cell patients

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Abstract: Background: Sickle cell patient population in the U.S. continues to increase due a combination of birth of sickle cell disease infants, extension of lifespan of existing patients and also possibly, a contributing immigration component. These factors and most importantly the latter, might be altering national estimates by both underestimating the number of affected individuals as well as underestimating the impact of public health strategies given the estimates for which there were conceived. Methods: National sickle cell disease estimates as per Centers for Disease Control (CDC) and immigrant population trends obtained from the U.S. Census Bureau from years 2010-2017 were examined. Immigrant groups from geographical regions highly prevalent for sickle cell disease were evaluated throughout this period of time. Results: From years 2010 to 2017 Western Africa (Nigeria, Ghana, Cape Verde, Liberia, Sierra Leona), showed a population increase of 45.2%, 44.15%, 24%, 19.0% and 16.3% respectively. Eastern Africa (Ethiopia, Kenya and Eritrea) had a population increase of 55.7%, 46.8% and 65% respectively. Caribbean island (Dominican Republic, Haiti and Jamaica) showed an increase of 31.8%, 18.6% and 46.8% respectively. Extrapolation of the prevalence in these populations shows that the sickle cell disease prevalence is likely higher than what is reported in US. Conclusions: The complexities of reaching an estimated number may be more challenging in an ever-changing and growing population. More so considering the different situations behind the immigration of each group and the migratory status which might be inducing an underestimation of the sickle cell population in the U.S. This study attempts to shed light on factors that may be skewing previous statistical estimates. Examining the migratory aspects inducing possible statistical bias may contribute to further address this disease encompassing this population's growth rate into prospective public health strategies to a more comprehensive approach to the disease.

Keywords: Allele, HgbSS, HbSC, sickle ß$^{+}$ thalassemia, sickle ß^{0} thalassemia

Introduction

During the last four decades high income countries have seen a shift in sickle cell disease mortality trends and survival. While it is still a significant cause of early children mortality in sub-Saharan Africa where sickle cell disease is the greatest public health burden, over 95% of individuals with the diagnosis survive to 18 years in the United States (U.S.) [1, 2]. In the U.S. public health measures like newborn screening, prophylactic antibiotics, Streptococcus. pneumoniae vaccination, management of acute pain events and the addition of hydroxyurea during the last two decades has changed the perspective from a previously life-threatening disease in children, to what is now a chronic disease [2]. In recent years adult life expectancy has increased to approximately 54 years [3]. As a public health priority declared by the World Health Organization, comprehensive strategies to address the disease had been key to changing the disease profile in the U.S. and other high income countries.

Despite medical advancements and increased focus by public health strategies resulting in decreased sickle cell-related morbidity and mortality in the U.S, its social complexity still pose a challenge for medical management. While newborn screening has been paramount in early diagnosis and management, it is not straight forward to estimate the number of individuals with the disease [4]. Estimates are most likely highly underestimated, as the impact of immigration from countries and regions of high

Table 1. Foreign born population from sickle cell prevalent countries (Caribbean)

Year	Jamaica	Haiti	Dominican Republic
2010	641849	542091	802001
2011	654587	559331	833411
2012	671197	572896	866618
2013	686535	581724	906167
2014	697215	597650	942123
2015	708493	615300	979779
2016	714687	631992	1012296
2017	727634	643341	1057439

prevalence has not been determined in previous studies.

Over the last decade (2010-2018) sub-Saharan African population has markedly increased by 52%, representing now the fastest growing immigrant population in the U.S. Ghana, Nigeria, Ethiopia, Somalia, Democratic Republic of Congo are some of the main countries of origin of this growing population and these are also some of the countries with the highest prevalence of sickle cell disease [5]. In this study we discuss the possible effects of immigration on reported sickle cell disease incidence, prevalence and mortality estimates.

Methods

Data source

Data from the Census Bureau (years 1990-2017) and Centers for Disease Control on sub-Saharan and Caribbean immigration groups during years 2008-2013 was analyzed to examine trends. These are also the regions with the highest prevalence of sickle cell disease. Population estimates incidence, prevalence and mortality trends in the U.S. over the last 20 years was compared in view of immigration patterns of the last decade. Results on these three parameters reported in studies from New York (years 2000-2008) and Michigan (years 1997-2014) were also considered as well as race, ethnicity and nativity [6, 7]. Prevalence in the countries of Nigeria, Ghana, Cape Verde, Liberia, Sierra Leona, Ethiopia, Kenya and Eritrea Dominican Republic, Haiti and Jamaica was extracted from published literature [8-10]. The data from the CDC and U.S census Bureau is publicly available and does not contain any identifying information, making this retrospective study exempt from review by the Institutional Review Board. The retrospective nature of studying de-identified patient data, lack of direct patient contact or intervention also makes this study exempt for ethics committee and from the requirement of patient consent.

Statistical analysis

T test using excel software by Microsoft has been used to analyze the data. It was used to test sample populations and determine if there was a significant difference between their means. Comparison between different groups were made and values with $P < 0.05$ were deemed to be statistically significant and independent.

Results

Population increase by geographical area

Recent decades had shown a population increase in the U.S, more prominent with descent from sub-Saharan African countries. Advances in medical care, improvement in availability of medical care, introduction of new therapeutics etc. have resulted in an improvement in life expectancy in these countries. Along with the increase in the general population, the fractions of patients who have sickle cell disease has also increased. Hence it is important to note that the chances of patients with sickle cell disease who may immigrate has also slowly increased over time. Such countries, especially those in the Eastern and Western African regions had shown the greatest population increase during 2010-2017, as estimated by the U.S. Census Bureau. Caribbean countries where sickle cell disease is most prevalent (Dominican Republic, Haiti and Jamaica) had shown an increase percent of 31.8%, 18.6% and 46.8% respectively which is depicted in **Table 1**. A comparison between the Caribbean countries is shown in **Figure 1** and statistical significance of $P < 0.05$ is denoted by *. The exact values for Dominican Republic vs. Haiti and Jamaica for the years 2010 to 2017 are: 0.00000; 0.00001; 0.00003; 0.00007; 0.00028; 0.00159 and 0.01632. **Table 2** shows Eastern Africa composed of Ethiopia, Kenya and Eritrea which had a population increase percentage of 55.7%, 46.8% and 65% respectively. **Figure 2** shows the comparison of these populations between the Eas-

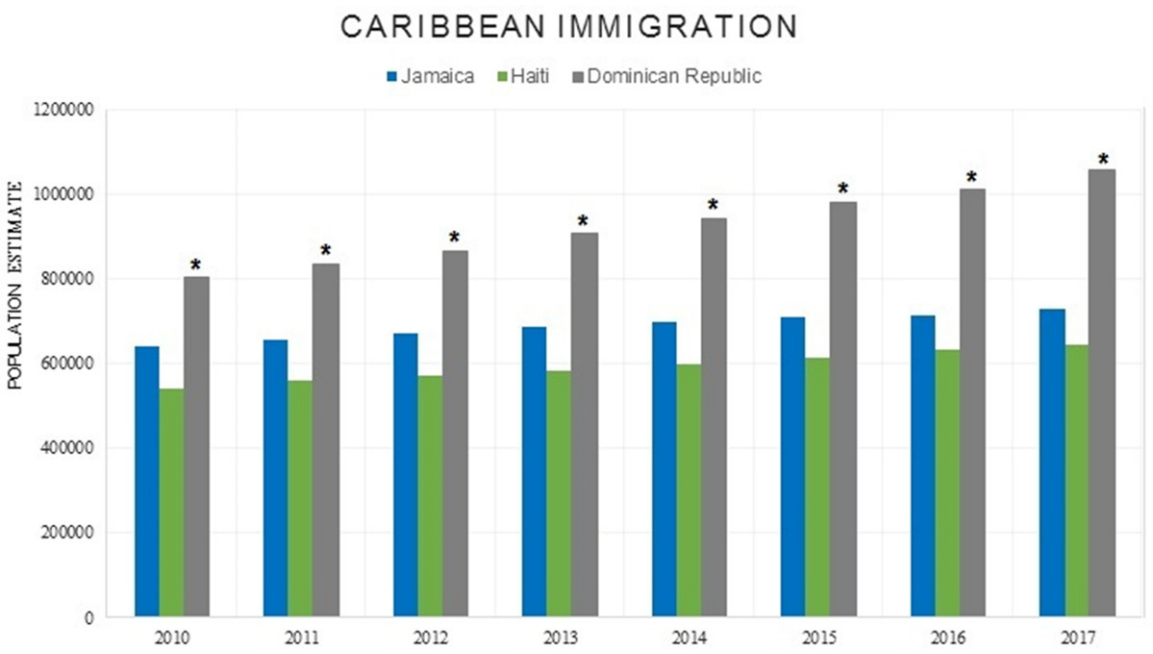

Figure 1. Foreign born population from sickle cell prevalent countries (Caribbean). * denotes statistically significant difference between Dominican Republic vs. Jamaica and Haiti for each year from 2010 to 2017, P < 0.05.

Table 2. Foreign born population from sickle cell prevalent countries (Eastern Africa)

Year	Ethiopia	Kenya	Eritrea
2010	145243	85385	23355
2011	151515	90087	25848
2012	164046	95126	27148
2013	177234	101577	29188
2014	188061	105453	30948
2015	199676	112857	32754
2016	215060	119334	34392
2017	226159	126209	38657

tern African countries and statistical significance of P < 0.05 is denoted by *. The exact values for Ethiopia vs. Kenya and Eritrea for the years 2010 to 2017 are: 0.00000; 0.00000; 0.00000; 0.00001; 0.00007; 0.00057; 0.00591 and 0.00032. Western Africa composed of Nigeria, Ghana, Cape Verde, Liberia, Sierra Leona, demonstrated a population increase percent of 45.2%, 44.15%, 24%, 19.0% and 16.3% respectively as shown in **Table 3**. Similarly, **Figure 3** shows the comparison between Western African countries and statistical significance of P < 0.05 is denoted by * and #. The exact values for Nigeria vs. Liberia, Ghana and Sierra Leona are: 0.00000; 0.00000; 0.00000; 0.00003; 0.00017; 0.00111 and 0.01332. The exact values for Nigeria vs. Cape Verde are: 0.00000; 0.00000; 0.00000; 0.00002; 0.00015; 0.00097 and 0.01260.

Prevalence of sickle cell disease in emigrant nations

Table 4 shows that the prevalence of sickle cell disease from these countries based on prevalence and the sum amount to more than 194000 patients. Even factoring for a circumstances where the immigrant population does not remain homogenous and assuming that only 1 in 10 of patients with sickle cell disease emigrated, the resultant figure of approximately 20,000 patients represents 20% correction factor for the reported 100,000 patients in US. This estimate may not be consistent across all the regions/countries described but it does highlight the significant contribution of the immigrant population to the current pool of sickle cell patients in the United States. Recently there has been a legislative effort to decrease the immigration of patients who may be a burden on the health care system in the United States ("public charge"). Such efforts may decrease the influx of immigrants with sickle cell disease in the future but the current estimate of sickle cell patients in the United

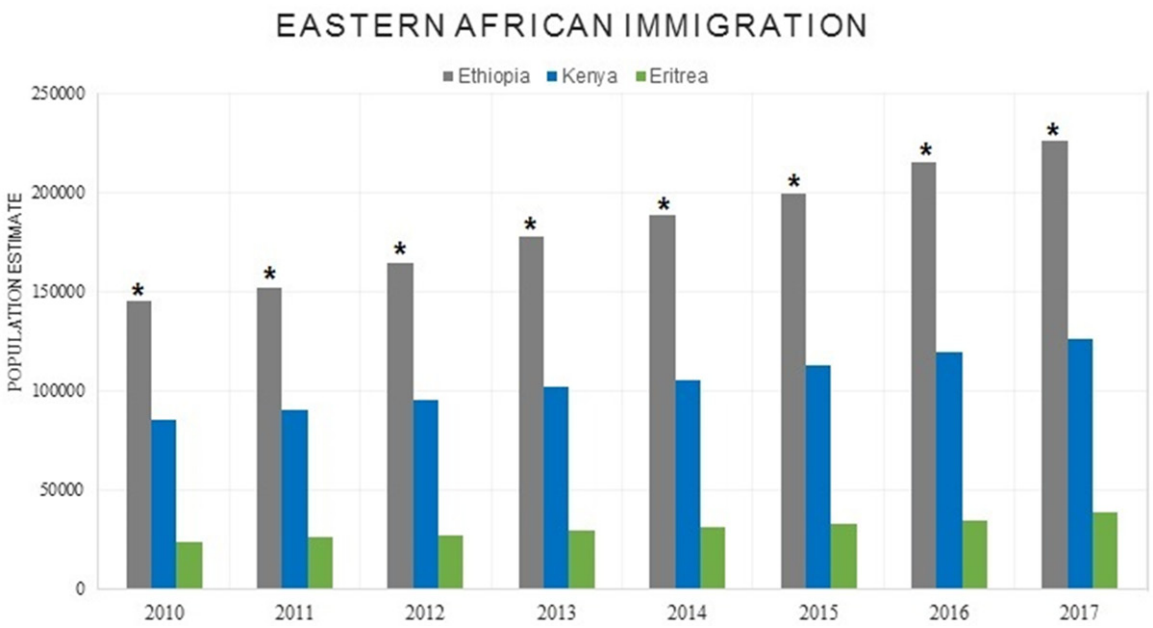

Figure 2. Foreign born population from sickle cell prevalent countries (Eastern Africa). * denotes statistically significant difference between Ethiopia vs. Kenya and Eritrea for each year from 2010 to 2017, $P < 0.05$.

Table 3. Foreign born population from sickle cell prevalent countries (Western Africa)

Year	Nigeria	Liberia	Ghana	Sierra Leona	Cape Verde
2010	205519	69911	110298	32880	32084
2011	210470	71038	116807	34161	33119
2012	221077	71062	120785	34588	34678
2013	228471	72627	129383	35213	35213
2014	238599	74737	136967	36584	35293
2015	258540	77064	145218	37595	36507
2016	277027	79974	152058	37675	38036
2017	298532	83221	158999	38257	39836

States likely represents an underestimation of the prevalence of sickle cell disease.

Discussion

National and state population estimates for sickle cell disease in the U.S. have proven to be an elusive but critical piece of information as key economic, political and healthcare initiatives stem from adequate assessment of disease burden [12]. As a consequence of combined efforts from newborn screening, prophylactic antibiotics and vaccinations, as well as hydroxyurea therapy approved in 1998 for adults with sickle cell disease, an evident shift in life expectancy has been observed over recent decades [12]. Although in 1970 a child born with the diagnosis was predicted to die before 5 years of ages, now more than 95% reach adulthood. This has directly contributed to the increase in prevalence as sickle cell anemia population since in early 1980s was estimated around 32,000 to 50,000 and currently is estimated around 100,000 individuals in the U.S. [11].

It is important to consider the immigrant population from countries and regions where sickle cell disease is prevalent as it might contribute to the ever-changing national landscape of the disease [12-14]. Incidence, prevalence and mortality in sickle cell estimates have been likely underestimated as a consequence of the on-going migratory effect, quickly out-dating the information assessed and reported. On another note, efforts from public health agencies to address and prioritize the disease with large scale strategies although demonstrating improvement, might be falling short in part as a result of the challenges posed by progressive immigration element difficult to capture in estimates.

Migratory effect of U.S. born sickle cell disease individuals and foreign-born citizens relocating to different states and metropolitan areas, create specific regional needs possibly requiring a

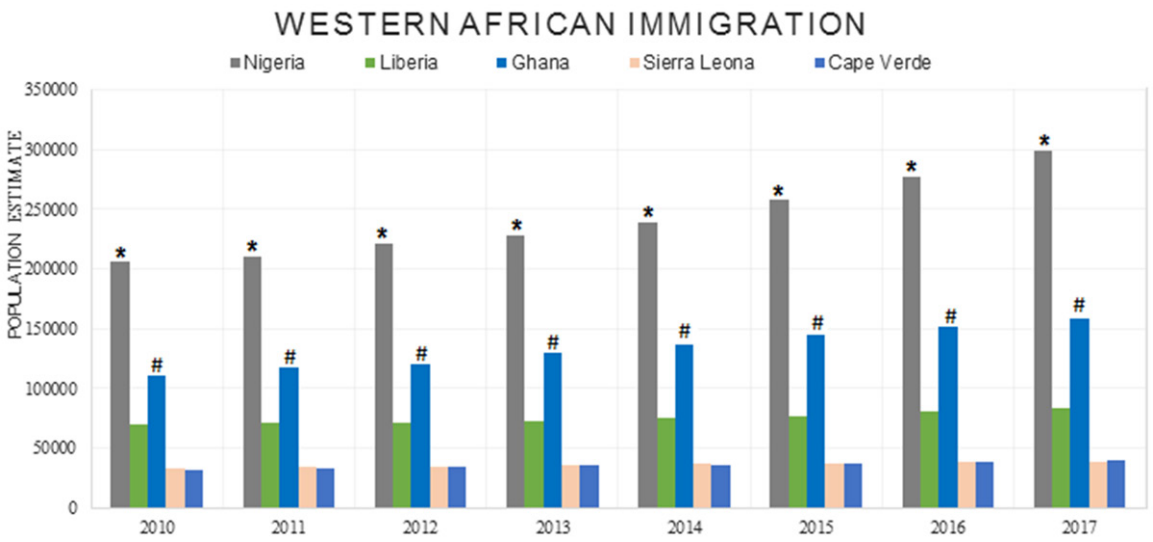

Figure 3. Foreign born population from sickle cell prevalent countries (Western Africa). * denotes statistically significant difference between Nigeria vs. Liberia and # denotes statistically significant difference between Ghana vs. Sierra Leona and Cape Verde for each year from 2010 to 2017, $P < 0.05$.

Table 4. Estimated cases of sickle cell disease in immigrant population based on prevalence

Serial No	Country	2017 US census	Prevalence	Estimated cases
1	Ethiopia	226159	0.05	11308
2	Kenya	126209	1	126209
3	Eritrea	38657	0.025	966
4	Nigeria	298532	1.659	495265
5	Liberia	83221	0.5	41611
6	Ghana	158999	1	158999
7	Sierra Leona	38257	1.659	63468
8	Cape Verde	39836	4	159344
9	Jamaica	727634	0.66	480238
10	Haiti	643341	0.44	283070
11	Dominican Republic	1057439	0.12	126893

different local approach, although certain trends might be consistent across the nation. A study on incidence among newborns in New York State (from years 2000-2008) assessed maternal race, ethnicity and country of origin was assessed. This study reported a higher incidence of sickle cell disease in children born from foreign mothers when compared with US-born mothers and it was consistent among all races and ethnic groups (1:1,678 from US-born vs 1:716 from foreign-born) [6]. Overall among the foreign-born non-Hispanic black mothers they reported the highest incidence in those originally from Jamaica, Haiti, Ghana and Nigeria respectively. This correlates with national immigration trends obtained from the US Census Bureau 2010-2017 as these demonstrated the highest immigration increase percentage and these are also among the largest growing immigrant groups from their respective regions. In general terms sub-Saharan immigration increased by 52% during 2010-2018 surpassing the increase rate of overall foreign-born population in that timeframe, 81% coming from Eastern of Western Africa and the majority locating to Northeast US. From the Caribbean region the New York study reported lower incidence of sickle cell disease births from non-Hispanic black foreign-born mothers which included Jamaica, Antigua and Barbuda, Barbados and Haiti when comparing to African immigration [6]. The northeastern region of the U.S. shows the highest incidence of sickle cell disease among states as well as among the Hispanic population, which correlated with their Caribbean origin and African ancestry settling in that region. This in contrast to Hispanics from other countries of origin, located in other regions of the U.S. with other racial background. Importantly this study describes the four variants of sickle disease and reported higher frequency of hemoglobin S allele in newborns

from foreign born non-Hispanic black mothers of Caribbean, Western African or Central African origin. This may contribute to the national increase in population from these geographical regions of origin and the national increase in prevalence of the disease.

Despite the significant reduction in children mortality in the U.S. with reported 68% from 0-3 years, 39% from 4-9 years and 24% from 10-14 years of age during 1999-2000 by the CDC, mortality in adults has shown modest improvement. It is reasonable to consider that estimates on mortality and sickle cell derived comorbidities may be biased by the immigrant population with advanced stages of the disease. As new immigrant individuals with possibly different and limited management in their countries of origin are added to US estimates, it is probable that certain sickle cell derived comorbidities were at an advanced stage prior to relocating to the US. Of the four variants of sickle cell (HbSS, HbSC, sickle ß$^+$ thalassemia and sickle ß^0 thalassemia) HbSS is the most clinically severe and is also the most prevalent in Africa, consequently this could have a direct impact on the mortality of this specific immigrant population with sickle cell disease, skewing the overall national estimates and resulting in overestimation of mortality yet and underestimation of the true impact of national public health efforts in addressing sickle cell disease over the last two decades.

Among the limitations of this study is the absence of data and estimates on immigration after the year 2017 as well as more specific and recent data on sickle cell patient estimates other than overall prevalence. As sickle cell is not a reportable condition it is challenging to determine more accurately the number of immigrant population affected that have not been added to the national estimates, as well as their sickle cell derived comorbidities increasing mortality and possibly underestimating the true benefit of healthcare efforts in the net population before the added immigrant patients.

Conclusions

This study attempts to shed light on factors that may be skewing previous statistical estimates. Accounting for the contribution of immigrant population with high sickle cell prevalence, it appears that there are at least 20% more expected sickle cell patients than what are reported in the US. Immigration origin and its influence in national sickle cell disease incidence, prevalence and mortality estimates has been suggested in previous studies. However an evaluation correlating immigration trends from regions where sickle cell disease is prevalent and its association with sickle cell disease incidence, prevalence and mortality has not been described. Funding and strategic planning of initiatives geared to address the public health issue of sickle cell disease requires population estimate parameters. Accuracy of estimates face the challenge of underestimation due to rapidly ever-growing at-risk population. Examining the migratory aspect in more detail, as it is highly likely inducing possible statistical bias may contribute to further address the disease encompassing this growing population into prospective public health strategies.

Disclosure of conflict of interest

None.

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