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Global Thalassemia Epidemiology: A Systematic Literature Review

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BACKGROUND

- Alpha and beta-thalassemia are characterized by imbalanced globin chain production, resulting in ineffective erythropoiesis and hemolytic anemia.
- Patients with thalassemia intermedia or major may experience serious complications, including iron overload, osteoporosis, thrombosis, and increased risk of mortality.
- While thalassemias are common in areas historically endemic to malaria, the global epidemiology is changing due to factors such as population screening, improved survival rates, and migration.
- Comprehensive understanding of the global prevalence, particularly with region- and subtype-specific estimates, is limited. Previous undertakings[1,2] aimed at understanding global thalassemia prevalence have focused on birth prevalence and may not represent the present-day epidemiology of thalassemia. Additionally, while previous global reviews employed diligent efforts to include epidemiological data, they were not explicitly systematic.

AIMS

- To determine the global prevalence of alpha- and beta-thalassemia (excluding minor/trait types), and to identify critical evidence gaps.

METHODS

- A systematic literature review (SLR) was conducted. Excerpta Medica database (Embase) (**Table 1**), PubMed (via MEDLINE), and the Cochrane Library (Database of Systematic Reviews) were searched to identify real-world observational studies published from January 1, 2000 to June 15, 2020 reporting on the incidence and/or prevalence of thalassemia. Additionally, the following were also searched:
  - Reference lists of relevant SLRs, narrative reviews, and meta-analyses identified via the bibliographic database searches
  - Grey literature from the past 3 years (2017–2020) of all relevant conference abstracts indexed via Embase

Table 1. Search Strategy for Embase (via Embase.com; similar searches conducted in Medline and Cochrane Database of Systematic Reviews)

Database: Embase (via Embase.com)	Date of Search: June 15, 2020			
Search	**Query**			**Number of Records Found**
#1	'thalassemia'/exp OR thalassemia:ab,ti OR thalassaemia:ab,ti OR 'cooley anemia':ab,ti OR 'cooley anaemia':ab,ti OR 'cooley disease':ab,ti OR ((cooley*:ab,ti OR cooleys:ab,ti) AND (anemia:ab,ti OR anaemia:ab,ti OR disease:ab,ti))			38,044
#2	'prevalence'/exp OR prevalence:ab,ti OR prevalent:ab,ti OR 'incidence'/exp OR incidence:ab,ti OR incident:ab,ti OR 'epidemiologic data'/exp OR epidemiology:ab,ti OR surveillance:ab,ti OR morbidity/exp			2.9m
#3	#1 AND #2			6,742
#4	'family study'/exp OR 'longitudinal study'/exp OR 'longitudinal study':ab,ti OR 'longitudinal studies':ab,ti OR 'retrospective study'/exp OR 'retrospective studies':ab,ti OR "retrospective study':ab,ti OR (('prospective study'/exp OR 'prospective studies':ab,ti OR 'prospective study':ab,ti) NOT 'randomized controlled trial'/exp) OR ((cohort NEAR/1 (study OR studies)):ab,ti) OR (('follow up' NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti) OR ((epidemiolog* NEAR/1 (study OR studies)):ab,ti) OR (('case control' NEAR/1 (study OR studies)):ab,ti) OR ((observational NEAR/1 (study OR studies)):ab,ti) OR 'real-world':ab,ti OR database:ab,ti OR register/exp OR registy:ab,ti OR registries:ab,ti OR ((chart NEAR/1 (review OR reviews)):ab,ti)			2.9m
#5	#3 AND #4			1,577
#6	#5 NOT letters or editorials	#5 NOT (letter:it OR editorial:it)		1,560
#7	#6 NOT animal studies	#6 NOT ('animals'/exp NOT 'humans'/exp)		1,556
#8	#7 NOT conference abstracts published in 2016 or earlier	#7: [conference abstract]/lim AND [1947-2016]/py	#8: #6 NOT #7	1,190
#9	#8 NOT narrative reviews or expert opinions	#9: #8 NOT ([review]/lim NOT (systematic OR (meta AND analy*)))		1,148

Key: exp – explode; it - publication type; lim – limit; py – publication years; ti,ab – title, abstract.

- Dual independent screening was performed, with disagreements resolved by a third researcher.
- Data extraction was performed by a single reviewer, with full validation by a second reviewer.

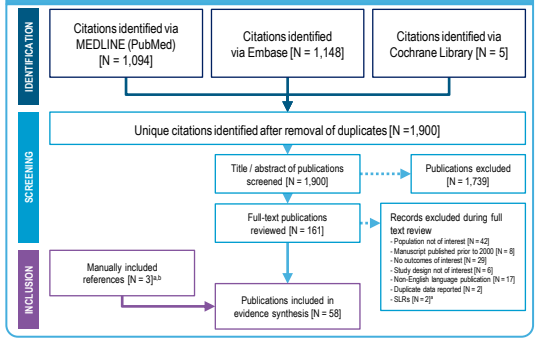
Calculations

- To estimate the prevalence of thalassemia in the European Union (EU, plus the UK; EU28) and other countries, prevalence estimates found in the SLR were applied to the 2019 population size of the respective countries. When country-level prevalence was not explicitly reported in a given paper, prevalence per 100,000 people was estimated from the reported data and then applied to the respective country's 2019 population size, which was retrieved from internet sources (2019 was available at the time of calculation). Results were also extrapolated to estimate the number of patients with thalassemia in the EU5 (France, Germany, Italy, Spain, the UK) as well as the United States (US).
- The median prevalence was calculated across the estimates found in EU28 countries in the SLR, and applied to EU countries for which prevalence estimates were not found in the literature. An exception to using the median was in the calculation for Cyprus, where the median prevalence yielded an unrealistically low estimated number of individuals with thalassemia. Thus, for Cyprus, the prevalence estimated in the Thalassaemia International Federation's report [20] was used.
- An additional calculation was undertaken to refine the estimated prevalence of thalassemia in the US. Specifically, data from a study by Hulihan et al [6] in which thalassemia prevalence, based on the state-based newborn screening programs, as well as supplementary sources, was reported for 6 US states (California, Florida, Georgia, Michigan, New York, North Carolina), were extrapolated to the whole US population. US census data from 2017 (the latest available at the time of the calculation) were used to calculate the total number of Black, Asian, or Hispanic individuals (ie, populations at higher risk for thalassemia) in each state and in the entire US; from there, the proportion of individuals from at-risk racial/ethnic demographic groups residing in each state was calculated. The prevalence of thalassemia that was reported for each of the 6 states in the Hulihan et al analysis was applied to the remaining 44 states using the prevalence estimate from the state from the Hulihan et al study with the closest at-risk racial/ethnic proportion. The estimated number of individuals with thalassemia was then summed, and that total was divided by the US population to estimate the prevalence of thalassemia in the US in 2017.

RESULTS

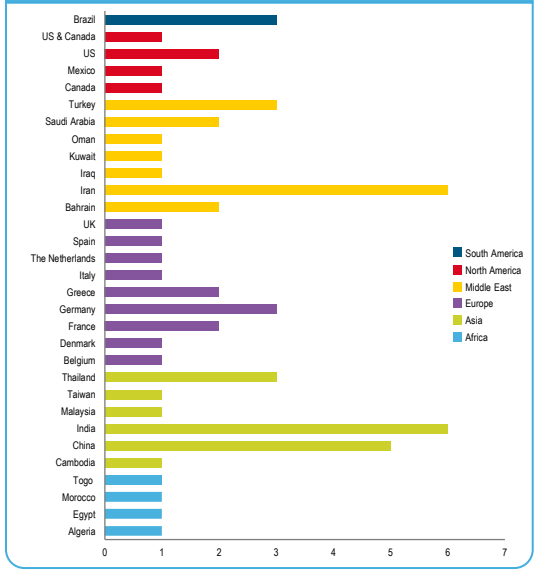
- Of 1,900 records screened, 58 publications met the protocol-defined selection criteria for inclusion in the SLR (see **Figure 1** and **Figure 2**).
- Population-based prevalence data were reported in 17 studies from North America, Europe, the Middle East, and North Africa[3-19] (see **Figure 3**).

Figure 1. Literature Selection and Review Process



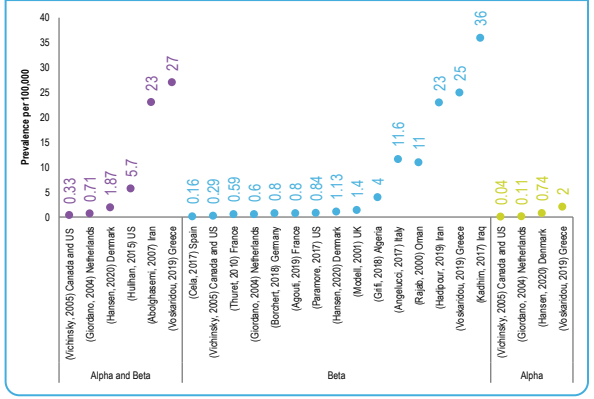
* The reference lists of included SLRs were manually searched for any additional relevant studies. Two studies were identified for inclusion.
† One additional conference poster (Agouti 2019) was manually identified for inclusion.
Key: SLR – systematic literature review.

Figure 2. Included Studies by Country



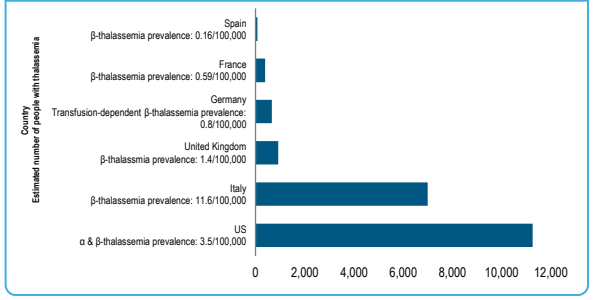
Key: UK – United Kingdom; US – United States.

Figure 3. Prevalence Estimates of Thalassemia Reported in Population-Based Studies



- For most countries with population-based studies, prevalence data were reported for beta-thalassemia only (in 8 of the 14 countries with population-based estimates).
- In the US, the estimated population-based prevalence of alpha- and beta-thalassemia combined was 5.7/100,000 when using a crude extrapolation from the Hulihan et al study.[6] When using a more refined calculation that accounted for differing distribution of individuals from at-risk racial/ethnic groups across states, the estimated prevalence of thalassemia was 3.5/100,000 in 2017.
- In Europe, the estimated beta-thalassemia prevalence (9 studies [8 countries]) ranged from 0.16/100,000 in Spain to 25/100,000 in Greece; alpha-thalassemia prevalence (3 studies/countries) was low, ranging from 0.11/100,000 in the Netherlands to 2/100,000 in Greece.
- Extrapolation calculations estimated the prevalence of thalassemia in the EU28 to be 3/100,000 people in 2019. In the EU5, prevalence ranged from 0.16/100,000 in Spain to 11.6/100,000 in Italy (see **Figure 4**).
- In a single population-based analysis from North Africa, the prevalence of beta-thalassemia was 4/100,000 in Algeria, and across the Middle East (3 studies), the prevalence of beta-thalassemia ranged from 11/100,000 in Oman to 36/100,000 in Iraq.
- Thalassemia prevalence data from Africa, Asia, and South America were mainly limited to specific sites or study samples that may not be generalizable to the respective countries within those regions. Further, the prevalence results ranged widely, indicating potential selection bias in these non-population-based studies.

Figure 4. Estimated Number of Individuals With Thalassemia by Country in 2019 (EU5 and US)



Key: α – alpha; β – beta; US – United States.

LIMITATIONS

- In this SLR, thalassemia prevalence data were only found for 8 of the 28 EU countries. For the remaining 20 countries, the median prevalence from the 8 countries (+ Cyprus) was used. The countries for which data were found tended to be ones with relatively low risk of thalassemia, and 5 of the 8 countries only had beta-thalassemia data. Therefore, the median (1.4) is possibly an underestimate in some countries. Raising the median to 4.0 resulted in 23,320 thalassemia patients and a prevalence of 4.54/100,000 or 0.454/10,000. Even with the limitations, the prevalence of thalassemia is expected to be well below the 5/10,000 threshold defining a rare condition in the EU.
- Key evidence gaps in the published literature included incomplete reporting of thalassemia subtypes, lack of diagnosis confirmation, and a paucity of recent, population-based analyses, including from countries with thalassemia registries.

CONCLUSION

- **Based on available published data, the estimated prevalence of thalassemia (excluding minor/trait types) varied globally, with highest prevalence in Greece and the Middle East, and lowest prevalence in the Netherlands, Spain, France, and Germany.**
- **There are limited prevalence data in non-Western countries, and in alpha-thalassemia in general.**
- **Additional studies, including global and country-specific thalassemia registries, are needed to better understand the current prevalence of this condition.**
- **The evidence compiled in this SLR support thalassemia being a rare condition (ie, <5/10,000 in the EU and <200,000 people in the US).**

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