Global Health Burden of Haemoglobinopathies

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XXIXth International Symposium on Technological Innovations in Laboratory Hematology, Milan, Italy, 12 May 2016
Financial disclosure

None
Haemoglobinopathies

**Structural haemoglobin variants**
- Hemoglobin S
- Hemoglobin C
- Hemoglobin E

**Thalassemia syndromes**
- α-thalassemia
- β-thalassemia

Most common monogenic diseases, ~7% of humans are carrying one of the genetic mutations responsible for these disorders.

+ all protective against malaria
Global Distribution

A

Hemoglobin S
- <10%
- >10%

Hemoglobin C

Hemoglobin E

B

α-Thalassemia
- α^0-thalassemia
- α^+ -thalassemia

β-Thalassemia
Global Distribution

Malaria endemcity
- Malaria free
- Epidemic
- Hypoendemic
- Mesoendemic
- Hyperendemic
- Holoendemic

Increasing health burden?

- How to quantify a disease burden?
- How to quantify changes in disease burden?
Global Health Burden

• There is a growing international effort to **quantify** the global burden of diseases to both define public health priorities and assess progress.

• The precision and reliability of any **estimates** depends on the availability of basic epidemiological data (e.g. prevalence, allele frequency).

• New epidemiological data is necessary to identify **temporal** and **spatial** changes.

• Remarkable geographical **heterogeneity** in the frequency of haemoglobinopathies.
Modell & Darlison’s estimates (WHO)

• Largely based on Livingstone’s unique database published 1985.

• Basic methods.
  • Data from single small survey often extrapolated to an entire country.
  • Does not include any estimation of the precision of the estimates (e.g. confidence intervals, uncertainty).

• Remains the only comprehensive source of estimates for all haemoglobinopathies.
**Piel et al’s estimates (MAP)**


- Based on i) up-to-date data extracted from **systematic reviews of the literature** and inclusion of unpublished data (e.g. MalariaGEN Consortium)
Piel et al’s estimates (MAP)

• Based on ii) **Bayesian geostatistical methods**, i.e. probabilistic framework (assessing uncertainty) to calculate estimates in areas with no data based on the density and size of existing surveys.

<table>
<thead>
<tr>
<th>WHO regions</th>
<th>Population (in thousands)</th>
<th>CBR</th>
<th>Mean</th>
<th>Median</th>
<th>IQR</th>
<th>%</th>
<th>WHO</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFRO</td>
<td>888,817</td>
<td>0.0357</td>
<td>239,547</td>
<td>238,083</td>
<td>224,003</td>
<td>253,047</td>
<td>75.6</td>
</tr>
<tr>
<td>AMRO</td>
<td>939,833</td>
<td>0.0162</td>
<td>13,708</td>
<td>13,104</td>
<td>11,126</td>
<td>15,610</td>
<td>4.6</td>
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<tr>
<td>EMRO</td>
<td>560,803</td>
<td>0.0249</td>
<td>10,007</td>
<td>8,239</td>
<td>6,012</td>
<td>11,950</td>
<td>3.6</td>
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<tr>
<td>EURO</td>
<td>893,002</td>
<td>0.0123</td>
<td>3,653</td>
<td>3,271</td>
<td>2,408</td>
<td>4,370</td>
<td>1.3</td>
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<tr>
<td>SEARO</td>
<td>1,789,082</td>
<td>0.0200</td>
<td>44,132</td>
<td>42,597</td>
<td>35,022</td>
<td>50,750</td>
<td>15.1</td>
</tr>
<tr>
<td>WPRO</td>
<td>1,840,667</td>
<td>0.0128</td>
<td>4</td>
<td>9</td>
<td>2</td>
<td>3</td>
<td>0.0</td>
</tr>
</tbody>
</table>

0 In thousands
1 Crude birth rate
2 IQR
3 HbSS newborn estimates from Modell and Darlison, 2008
The Global Burden of Diseases, Injuries and Risk Factors Study (GBD) is a comprehensive regional and global assessment of mortality and disability from major diseases, injuries, and risk factors. GBD is a collaboration of over 1,000 researchers representing over 300 institutions and 50 countries.

Started in the 1990s; updated in 2010 (GBD2010) and 2013 (GBD2013); from now on on an annual basis (GBD2015, GBD2016,...).

Includes haemoglobinopathies since GBD2010.

Included sub-national data for a few countries in the GBD2013 (incl. UK and China).

Using complex modelling algorithm developed for all diseases together, rather than each disease individually.

Hardy-Weinberg Equilibrium

**Bi-allelic system (HbA & HbS):** \( p^2 + 2pq + q^2 = 1 \)

where \( p \) is the frequency of HbA and \( q \) is the frequency of HbS \((p + q = 1)\).

**Tri-allelic system (HbA, HbS & HbC):** \( p^2 + 2pq + q^2 + 2pr + r^2 + 2qr = 1 \)

**HWE assumptions:**
- organisms are diploid.
- only sexual reproduction occurs.
- generations are non overlapping.
- mating is random.
- population size is infinitely large.
- allele frequencies are equal in the sexes.
- there is no migration, mutation or selection.
Hardy-Weinberg Equilibrium

Angola
Kagane (2010) n = 30,453
Burkina Faso
Kabu, (2005) n = 2,341
Burundi
Muleza (2007) n = 857
DRC
Mulena (2007) n = 84
DRC*
Tshibola (2008) n = 4,116

Ghana*
Ohene-Frempong (Pers.com) n = 343,355
Mali
Diallo (2008) n = 1,029
Nigeria*
Kukani (1966) n = 700
Nigeria
Oladunmoye (2008) n = 644

Piel et al (2016) GIM
Spatio-temporal changes

1. Population growth

WHO 1994: 2.3% of world population carrying sickle haemoglobin

<table>
<thead>
<tr>
<th>Year</th>
<th>Global population</th>
<th>%</th>
<th>With HbS</th>
<th>%</th>
<th>With HbS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1994</td>
<td>5,661,086,346</td>
<td>2.30%</td>
<td>130,204,986</td>
<td>2.30%</td>
<td>130,204,986</td>
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<tr>
<td>1999</td>
<td>6,051,478,010</td>
<td>2.30%</td>
<td>139,183,994</td>
<td>2.50%</td>
<td>151,286,950</td>
</tr>
<tr>
<td>2004</td>
<td>6,435,705,595</td>
<td>2.30%</td>
<td>148,021,229</td>
<td>2.70%</td>
<td>173,764,051</td>
</tr>
<tr>
<td>2009</td>
<td>6,834,721,933</td>
<td>2.30%</td>
<td>157,198,604</td>
<td>2.90%</td>
<td>198,206,936</td>
</tr>
<tr>
<td>2014</td>
<td>7,243,784,121</td>
<td>2.30%</td>
<td>166,607,035</td>
<td>3.10%</td>
<td>224,557,308</td>
</tr>
</tbody>
</table>
Spatio-temporal changes

2. Epidemiologic transition

[Graph showing birth rate, death rate, and total population over time with different regions marked for under-five mortality rate.]

Spatio-temporal changes

3. Population migrations

Piel et al. (2014) The Lancet Global Health
Spatio-temporal changes

4. Population ageing

Sickle cell disease (US, UK, Jamaica)

We have more patients surviving
Patient population cohort, Malaysia 2002 → 2006 → 2010

- More children are surviving → adolescents → young adults
- Presence of more older patients
- Patient population cohort shifting to the right

Malaysia country report (2012)
Spatio-temporal changes

DALYs in 1-4 year olds

http://vizhub.healthdata.org/irank/arrow.php
Spatio-temporal changes

305,800 SCA births (CL 238,400 – 398,800)

404,200 SCA births (CL 242,500 – 657,600)

Future challenges

Diagnosis

- Most of the births affected by sickle cell disorders occur (and will occur) in sub-Saharan Africa (low-income countries).
- Most of the births affected by thalassaemia syndromes occur (and will occur) in Southeast Asia (middle-income countries).
- Affordable and reliable diagnosis is essential to collect epidemiological data and provide appropriate healthcare.
- Access to sequencing facilities or DNA testing is improving but is still limited in most low- and middle-income countries.
Future challenges

Increasing diversity of variants

Ten Years of Routine α- and β-Globin Gene Sequencing in UK Hemoglobinopathy Referrals Reveals 60 Novel Mutations

Shirley J. Henderson, Adele T. Timbs, Janice McCarthy, Alice E. Gallienne, Melanie Proven, Michelle J. Rugless, Herminio Lopez, Jennifer Eglington, Dariusz Dziedzic, Matthew Beardsall, Mohamed S.M. Khalil & John M. Old

Clinical and Laboratory Observations

A Novel Sickle Hemoglobin: Hemoglobin S-South End

Hong-yun Luo,*† Adeboye H. Adeyowe,† Shawn H. Eung,‡ Timothy P. Skelton,‡ Karen Quillen,‡ Lillian McMahon,‡ Martin H. Steinberg,‡† and David H. K. Chiu*†‡

Case Report

HbD Punjab/HbQ India Compound Heterozygosity: An Unusual Association

Stacy Colaco, Reema Surve, Pratibha Sawant, Anita Nadkarni, Kanjaksha Ghosh and Roshan Colah

National Institute of Immunohematology, Indian Council of Medical Research, 13th Floor, New Multistoried Building, King Edward Memorial Hospital Campus, Parel, Mumbai – 400012

Clinical Study

Current Genetic Epidemiology of β-Thalassemias and Structural Hemoglobin Variants in the Lazio Region (Central Italy) Following Recent Migration Movements

Antonio Amato,1 Maria Pia Cappabianca,1 Alessia Colosimo,2 Maria Perr,1 Paola Grisanti,1 Ivo Zaghis,1 Donatella Ponzini,1 and Maria Lerone1
Future challenges

European migrant crisis

Top Countries of Origin
- Syria
- Iraq
- Afghanistan
- Iran
- Iran
- Pakistan
- Somalia
- Sudan
- Nigeria
- Eritrea

Number of asylum seekers per month

Number of refugees

Europe's refugee crisis
Key Learning Objectives

1. Like other non-communicable diseases, haemoglobinopathies represent an increasing global health burden.

2. Population migrations, including the European migration crisis, have a long-term impact on the distribution and burden of haemoglobinopathies, outside malarious areas.

3. The vast majority of patients affected by sickle-cell disease and thalassaemias are in sub-Saharan African and Southeast Asia, respectively.

4. Reliable spatial and temporal epidemiological data are required in order to define adequate and sustainable health policies.

5. New low-cost reliable diagnostic methods are emerging and could lead to significant advances in the quantification of the burden of haemoglobinopathies in low- and middle-income countries.
Acknowledgements

Main collaborators

- Prof David Weatherall (UK)
- Prof Sunetra Gupta (UK)
- Dr Bridget Penman (UK)
- Carinna Hockham (UK)
- Prof Tom Williams (UK/Kenya)
- Prof David Rees (UK)
- Prof Baba Inusa (UK)
- Dr Scott Grosse (US)
- Dr Tom Adamkiewicz (US)
- Prof Simon Hay (UK/US)
- Dr Rosalind Howes (UK)
- Prof Andy Tatem (UK)

+ Local collaborators in more than 30 countries.

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