Institution: King's College London		
Unit of Assessment: UoA2		
Title of case study: Sickle Cell Disease: Globalising and extending population screening and black and ethnic minority health		
Period when the underpinning research was undertaken: 2000 – 2020		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
Streetly	Senior Lecturer	1997 – present
Dormandy	Research Fellow	1999 – 2013
Marteau	Professor	1993 – 2012
Gulliford	Professor	1988 – present
Period when the claimed impact occurred: August 2013 – December 2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact

Haemoglobin disorders predominantly affect black and ethnic minority groups, contributing to inequalities in health. Since 2000, King's College London research identified the effectiveness of implementing antenatal and newborn screening for sickle cell disease and led the implementation of the national NHS screening programme. In the period from 2013 to 2020, King's research informed the programme standards for timely haemoglobinopathy screening of all pregnant women and newborn infants in the UK. Internationally, King's researchers contributed to the 2018 Pan-European Consensus Statement on newborn sickle cell screening, which recommended other countries to adopt the NHS model led by King's. In 2015/16, King's researchers supported the design and implementation of the first pilot programme for newborn sickle cell screening in Tanzania.

2. Underpinning research

Sickle Cell Disease and Thalassaemia.
Haemoglobin disorders, including sickle cell disease and thalassaemia, are the most common genetic disorders worldwide. They primarily affect black and ethnic minority populations and contribute to inequalities in health. King's REF2014 impact case study demonstrated the feasibility of introducing a newborn screening programme for sickle cell disease in the UK. Since 2000, King's research demonstrated the effectiveness and impact on informed choice of screening for haemoglobin disorders early in pregnancy.

King's research shows sickle cell carriers may be identified very early in pregnancy.
Providing parents with informed choice over reproductive outcomes, requires that pregnancies affected by haemoglobin disorders are detected at a very early stage and ideally before 10 weeks gestation. King's researchers reported a study of 1,441 eligible women attending 25 general practitioner clinics offering universal antenatal screening in the UK. The study showed that screening tests for sickle cell or thalassaemia were performed at a median 6.9 weeks after the first pregnancy consultation ('booking visit'), with only 4.4% of women being screened before 10 weeks gestation **(1)**. To address this, the King's SHIFT cluster randomised trial showed that GP-led care, with sickle cell testing at the first pregnancy consultation, was effective at increasing early antenatal screening uptake with ≥20% more women taking up screening by 10 weeks gestation **(2 and 3)**. These results showed that offering antenatal screening for haemoglobin disorders as part of consultations for pregnancy confirmation in primary care substantially increases the proportion of women offered and taking up screening before 10 weeks gestation. This is important in enabling carrier couples to choose their preferred option very early in pregnancy. The King's

study found no evidence to suggest that early screening offers might impact negatively on parents' informed choice **(4).** Options may include prenatal diagnosis, with amniocentesis or chorionic villus sampling, leading to possible termination of pregnancy. King's research **(5)** subsequently provided a national evaluation of the NHS antenatal screening programme for haemoglobin disorders from 1 April 2007 to 31 March 2017. Based on data for 6,608,575 women, the research showed that programme coverage with antenatal tests and family origin questionnaire (used for initial screening in low prevalence areas) is now high.

King's research provided new evidence of the effectiveness of the national newborn screening programme for sickle cell disease.

King's national evaluation of the national NHS newborn sickle cell screening based on the blood spot programme in England **(6)** showed that the newborn screening programme identifies babies with sickle cell disease very accurately, with positive predictive value of 95% and specificity >99% (based on approximately 3.25 million screens). No missed cases were reported from testing during the period of the study, or over the previous decade, suggesting sensitivity near 100%. There were 80% of infants enrolled into specialist care by 3 months of age and almost all were seen by 6 months of age. Mortality is now low in children with sickle cell disease under the age of 5 years (1.7 per 1000 person-years) **(6)**.

Additionally, infants with sickle cell disease are at increased risk of invasive pneumococcal disease (IPD) as well as infections due to early onset of functional hyposplenism (reduced spleen function). King's research with Public Health England showed that most IPD cases are now due to serotypes not covered by the pneumococcal conjugate vaccine (PCV13), routinely offered to babies born in the UK **(7)**. Structured care ensures that affected infants receive penicillin prophylaxis and pneumococcal vaccination to protect against IPD. This research **(7)** recommended that healthcare professionals work more closely with families with sickle cell disease and local communities to emphasise the importance of penicillin prophylaxis and facilitate rapid access to healthcare for infections.

3. References to the research (indicative maximum of six references)

1. **Dormandy** E, **Gulliford** MC, Reid EP, Brown K, **Marteau** TM; SHIFT Research Team. Delay between pregnancy confirmation and sickle cell and thalassaemia screening: a population-based cohort study. Br J Gen Pract 2008; 58:154-9. doi: 10.3399/bjgp08X277267.

2. **Dormandy** E, Bryan S, **Gulliford** MC et al. Antenatal screening for haemoglobinopathies in primary care: a cohort study and cluster randomised trial to inform a simulation model. The Screening for Haemoglobinopathies in First Trimester (SHIFT) trial. Health Technol Assess 2010; 14:1-160. doi: 10.3310/hta14200.

3. **Dormandy** E, **Gulliford** M, Bryan S, Roberts TE, Calnan M, Atkin K, Karnon J, Logan J, Kavalier F, Harris HJ, Johnston TA, Anionwu EN, Tsianakas V, Jones P, **Marteau** TM. Effectiveness of earlier antenatal screening for sickle cell disease and thalassaemia in primary care: cluster randomised trial. BMJ 2010; 341:c5132. doi: 10.1136/bmj.c5132.

4. Brown K, **Dormandy** E, Reid E, **Gulliford** M, **Marteau** T. Impact on informed choice of offering antenatal sickle cell and thalassaemia screening in primary care: a randomized trial. J Med Screen. 2011;18:65-75. doi: 10.1258/jms.2011.010132.

5. Weil LG, Charlton MR, Coppinger C, Daniel Y, **Streetly** A. Sickle cell disease and thalassaemia antenatal screening programme in England over 10 years: a review from 2007/2008 to 2016/2017. J Clin Pathol 2020;73:183-190. doi: 10.1136/jclinpath-2019-206317

6. **Streetly** A, Sisodia R, Dick M, Latinovic R, Hounsell K, **Dormandy** E. Evaluation of newborn sickle cell screening programme in England: 2010-2016. Arch Dis Child. 2018; 103:648-653. doi: 10.1136/archdischild-2017-313213.

7. Oligbu G, Collins S, Sheppard C, Fry N, Dick M, **Streetly** A, Ladhani S. Risk of Invasive Pneumococcal Disease in Children with Sickle Cell Disease in England: A National Observational

Cohort Study, 2010-2015. Arch Dis Child. 2018;103:643-647. doi: 10.1136/archdischild-2017-313611

4. Details of the impact

King's contributes to the NHS haemoglobinopathy screening programme roll-out in England.

King's research has achieved impact through its contribution to design and roll-out the national NHS antenatal and newborn screening programmes for sickle cell disease and thalassaemia. King's hosted the new national NHS haemoglobinopathy screening programme centre, with Dr Allison Streetly as Programme Director, from 2003 to 2013 as outlined for REF2014 **(A)**. The continuing success of the sickle cell and thalassaemia screening programme has ensured that from 2013 to 2020, people with sickle cell disease and their families have continued to benefit from improved access to care. Individuals with sickle cell disease have benefited from earlier diagnosis soon after birth and more effective and equitable treatment. The NHS newborn screening programme, which King's evaluated in the present assessment period, ensures that an affected child can be diagnosed with sickle cell disease before presenting with symptoms or complications, providing an opportunity to ensure early entry into a systematic programme of preventive medical care. Newborn screening has increased the number of children being identified with sickle cell disease, in many areas almost doubling the service load. Under-ascertainment of the condition meant that the scale of need was previously under-recognised and deaths of infants with sickle cell disease contributed to higher infant mortality rates in urban areas as babies died without a diagnosis or treatment. A 2018 editorial in Archives of Disease in Childhood **(B)**, which commented on the King's evaluation, observed that 'England's newborn haemoglobinopathy screening system has demonstrated exceptional accuracy of detection and successful rates of patient notification, along with early intervention.'

King's research informs service standards for antenatal screening.

The linked NHS antenatal haemoglobinopathy screening programme ensures early detection of affected pregnancies giving affected couples informed choice over reproductive outcomes. Influenced by the results of King's SHIFT Trial, the national NHS Sickle Cell and Thalassaemia Screening Programme set programme standards **(C)** for timely antenatal screening including minimum standards of requiring 50% of women to receive their screening results by 10 weeks gestation, and for 50% of prenatal diagnosis procedures to be implemented by 12 weeks and 6 days gestation. The Data Report for 2016/17 **(D.4)** shows that the 53% of antenatal screening tests were completed by 10 weeks gestation in 2016/17 **(D.4 Table AN-9)**, but the proportion of pre-natal diagnosis procedures performed by 12 weeks and 6 days gestation decreased to 37% **(D.4 Table PND-1)**. Avoidable delays in screening and diagnosis confirmation, which King's research highlighted, can have a detrimental impact on people's lives, as shown through the recently published parents' stories from the Sickle Cell Society **(E)** about experiences of sickle screening in pregnancy. King's evidence contributed to the NICE (National Institute for Health and Care Excellence) Indicator CCG81 **(F)** for the proportion of pregnant women accessing antenatal care who are seen for booking by 10 weeks and 0 days. NICE Antenatal Guidance **(F)** now states that 'Screening for sickle cell diseases and thalassaemia should be offered to all women as early as possible in pregnancy (ideally by 10 weeks)', providing the standard for high quality care across the NHS in England.

Table 1: Haemoglobinopathy Screening Programme Impacts for England (Source D)				
	2013/14	2014/15	2015/16	2016/17
Newborn infants screened	668,117	661,432	667,800	667,521
Significant clinical condition	319	278	265	274
Carriers identified	8,850	8,942	8,579	8,530
Antenatal women screened	730,779	710,116	706,041	676,981
Screened by 10 weeks gestation	50%	51%	52%	53%
Screen positive sickle/thalassaemia	15,281	14,352	13,870	12,705
Father specimen received	9,687	9,129	8,655	8,688
High risk couples identified	944	822	772	751
Prenatal diagnosis (PND)	353	408	407	374
PND by 12 weeks 6 days	52%	40%	40%	37%
Affected foetus identified	89	118	104	80

The main impacts of the screening programme roll-out in this assessment period are summarised in Table 1, including results from the Screening Programme Data Reports from 2013/14 to 2016/17 **(D)**. In each year, more than 600,000 newborn infants and 650,000 pregnant women were screened. Screening led to the early detection of affected infants, enabling early delivery of evidence-based interventions, as well as the early detection of affected pregnancies, enabling informed parental choices. Carriers of the sickle cell trait have benefited through being enabled to make informed reproductive choices when a pregnancy may be affected.

King's provides international advice on haemoglobinopathy screening at the 2017 European Consensus Development Conference.

There has been international interest in the NHS screening programme, which is recognised to be the best developed in Europe, and arguably the world, providing a model for many other countries. King's researchers contributed to the 2017 European Consensus Development Conference in Berlin, with Dr Streetly being invited as a keynote speaker, which led to the publication of Pan European recommendations for newborn sickle cell screening, drawing on the UK model **(G)**. The consensus recommendations aimed to support the development of newborn screening programmes in health services of countries across Europe where they do not yet exist, and to assist quality improvement of existing programmes. The English NHS laboratory handbook, to which King's researchers contributed, was recommended as a guide for other countries **(G)**. An accompanying editorial **(H)** observed that 'This pan-European conference represents an important and pivotal first step towards wider newborn screening for the sickle haemoglobinopathies…There is an urgent need to develop and initiate universal screening programmes across Europe, particularly in light of the rapid globalization of migration flows, which lead to greater diversity among populations and higher prevalence of sickle cell disease.'

King's researchers supported the piloting and implementation of newborn sickle cell screening in Tanzania.

There is growing interest in screening for haemoglobin disorders in middle and low-income countries. Tanzania has the fifth highest incidence of sickle cell disease worldwide (with an estimated 11 000 sickle cell disease annual births). King's researchers helped to design a programme for sickle cell screening involving newborns at Muhimbili National Hospital (MNH) and Temeke Regional Hospital, Dar es Salaam, which was then implemented from January 2015 to November 2016 **(I)**. This much needed programme in Tanzania had support from the UK

Department for International Development. It adopted the newborn screening for sickle cell disease model from Public Health England and customised it to fit their settings. Muhimbili University of Health and Allied Sciences (MUHAS) conducted newborn screening for sickle cell disease in 2015/16 including 3,981 newborn infants. Sickle cell disease was diagnosed in 31 (0.8%) babies, with 505 (12.6%) identified with sickle cell trait **(I)**. This demonstrated the feasibility and outcomes of newborn sickle cell screening as a health program for sub-Saharan Africa and showed that sickle cell disease is a condition of public health importance in Tanzania.

Additionally, Dr Streetly's expertise was recognised in her appointment to the SAGE Ethnicity Subgroup **(J)** that advised on COVID-19 risks and impacts for minority ethnic groups (July 2020 – January 2021).

5. Sources to corroborate the impact

(A) Public Health Matters Blog Author Profile: Allison Streetly, Public Health England

(B) Editorial commentary on screening programme evaluation: Shook LM, Ware RE. Effective screening leads to better outcomes in sickle cell disease. *Archives of Disease in Childhood* 2018;**103**:628-630 [page 630]. (http://dx.doi.org/10.1136/archdischild-2017-314175)

(C) Guidance: Sickle cell and thalassaemia screening standards valid for data collected from 1 April 2018 - Published 1 March 2019, Public Health England

(D) NHS Sickle Cell and Thalassaemia Screening Programme Data reports and trends and performance analysis, Public Health England: D.1 2013/14; **D.2** 2014/15; **D.3** 2015/16; **D.4** 2016/17 - Table AN-9 and Table PND-1 [page 18 and 19]

(E) Sources that corroborate impact on parents' who have experienced sickle screening in pregnancy: E.1 PHE Screening Blog: Parents' stories: personal experiences of sickle cell and thalassaemia screening - 1 September 2017; **E.2** Parents' stories from the Sickle Cell Society Website

(F) Sources that corroborate NICE recommending screening for sickle cell diseases and thalassaemias to all women as early as possible in pregnancy (ideally by 10 weeks): F.1 NICE Indicator CCG81: Proportion of pregnant women accessing antenatal care who are seen for booking by 10 weeks and 0 days; **F. 2** NICE: Antenatal care for uncomplicated pregnancies (page 6); **F.3** PHE Screening Blog - Improving early access to sickle cell and thalassaemia screening - 21 September 2017

(G) Publication of Pan European recommendations for newborn sickle cell screening: Lobitz S, Telfer P, Cela E… **Streetly A**…et al. Newborn screening for sickle cell disease in Europe: recommendations from a Pan-European Consensus Conference. *Br J Haematol.* 2018;**183**:648-660. doi:10.1111/bjh.15600 [page 656] (https://onlinelibrary.wiley.com/doi/full/10.1111/bjh.15600)

(H) Editorial commentary on European Consensus Conference: Shook, L.M. and Ware, R.E. Sickle cell screening in Europe: the time has come. *Br J Haematol,* 2018;**183**: 534-535. doi:10.1111/bjh.15596 (https://onlinelibrary.wiley.com/doi/10.1111/bjh.15596)

(I) Source corroborating the implementation of newborn screening for sickle cell disease in Tanzania: Siana Nkya, Lillian Mtei, Deogratias Soka…**Allison Streetly**…Julie Makani, Newborn screening for sickle cell disease: an innovative pilot program to improve child survival in Dar es Salaam, Tanzania, *International Health* 2019; **11**: 589–595. https://doi.org/10.1093/inthealth/ihz028)

(J) Government Office for Science - Scientific Advisory Group for Emergencies: Transparency data List of participants of SAGE and related sub-groups - Updated 21 October 2020