Institution: University of Birmingham

Unit of Assessment: UoA1

Title of case study: Pulse Oximetry screening to detect heart disease in newborn babies

1. Summary of the impact (indicative maximum 100 words)

Congenital heart defects are a leading cause of infant death, accounting for more deaths than any other type of malformation and up to 7.5% of all infant deaths. Timely diagnosis is crucial for the best possible outcome for these children. However, the accuracy of current methods for screening for critical congenital heart defects (CCHD) before birth is variable and currently only detects these defects in between 35-50% of cases. Although around a third of remaining cases are picked up after birth, up to a third of children with a CCHD are sent home, where they may become unwell or die. Research led by Dr Andrew Ewer at the University of Birmingham has demonstrated that pulse oximetry is a rapid, safe, non-invasive, painless method of detecting the low blood oxygen levels associated with CCHD, and is also a cost-effective approach. As a result of Dr Ewer's research, Pulse Ox was recommended for adoption across the US in 2011 by the Secretary for Health and Human Services, and Dr Ewer has been instrumental in this screening approach being taken up worldwide. This research prompted a national UK review of screening for these conditions.

2. Underpinning research (indicative maximum 500 words)

Congenital heart defects (i.e. structural abnormalities existing at birth or during pregnancy) are the most common group of congenital malformations, accounting for 40% of all deaths from congenital malformations. These defects are a leading cause of infant deaths in the developed world, with most deaths occurring in the first year of life. Critical congenital heart defects (CCHD) occur in around 2/1000 babies, and are most likely to cause death. If they are not detected early, risk of circulatory collapse is increased, and although surgery can greatly improve survival, poor condition at presentation increases surgical mortality – hence timely diagnosis is crucial for the best outcome for these children. However, the accuracy of current methods for detecting CCHD is variable and only 35-50% of affected babies are identified before birth. Defects may be identified after birth, however around a third of babies with these potentially life-threatening defects in their hearts are discharged from hospital before diagnosis.

Blood oxygen levels are often low in CCHD. Pulse oximetry is a non-invasive method of measuring blood oxygen levels by placing a sensor on part of the patient's body. Although the technique itself was developed in the 1980s, and explored for CCHD identification in the 2000s, the results were inconclusive. Dr Andrew Ewer, Reader in Neonatal Paediatrics and at the University of Birmingham since 1995, led a team which conducted a systematic review (i.e. an exhaustive summary of all available research focusing on the technique) published in 2007 [1] which showed encouraging results but highlighted the difficulties in assessing the accuracy of pulse oximetry because of methodological variations, and importantly the relatively low numbers of patients studied. The systematic review demonstrated a clear need for a larger, robust, well-conducted study to confirm the accuracy, acceptability and cost effectiveness of such a screening test.

In 2007, the National Institute for Health Research funded the PulseOx study (NIHR HTA, £947k 2007-10, led by Ewer and run by the Birmingham Clinical Trials Unit). This large, multi-centre study assessed the accuracy of pulse oximetry for screening CCHDs in newborn babies. It was the largest UK study in this field, screening 20,055 newborn babies, and the first to assess the added value of pulse oximetry screening in modern healthcare systems where antenatal ultrasound screening was widely available. The study used robust methodology to generate precise estimates of the accuracy [2], cost-effectiveness and acceptability of pulse oximetry and the value added to existing screening [3]. These results demonstrated that the addition of pulse oximetry screening to existing screening tests resulted in 92% of babies with CCHDs being detected prior to discharge. In conclusion, the study found that pulse oximetry is a safe, feasible (i.e. easy to undertake and simple to adopt into routine practice) and acceptable test, complementing and adding value to existing screening where used in addition by identifying more issues at birth. The results of this study significantly enhanced available evidence indicating that pulse oximetry screening could be introduced as a routine procedure.

Dr Ewer's team also assessed the cost-effectiveness of utilising pulse oximetry screening in

combination with clinical examination in the early detection of potentially life-threatening CCHDs [4]. They demonstrated that the technique would identify 30 additional CCHD cases per 100,000 live births compared with routine clinical examination alone, with a very high likelihood (over 90%) that this would be regarded as 'cost-effective', i.e. worth the extra investment needed to identify these cases. A further systematic review in 2012 by Dr Ewer's team demonstrated that pulse oximetry met the criteria for routine screening which are set by the National Screening Committee [5,6].

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

1. Thangaratinam S, Daniels J, Ewer AK, Zamora J, Khan KS. Accuracy of pulse oximetry in screening for congenital heart disease in asymptomatic newborns: A systematic review. *Archives of Disease in Childhood: Fetal and Neonatal Edition* 2007;92(3):F176-F180. *http://dx.doi.org/10.1136%2Fadc.2006.107656*
2. Ewer AK, Middleton LJ, Furmston AT, Bhoyar A, Daniels JP, Thangaratinam Set al. Pulse oximetry as a screening test for congenital heart defects in newborn infants (PulseOx): a test accuracy study. Lancet 2011; 378(9793): 785-94. Epub 2011 Aug 4*. doi: 10.1016/S0140-6736(11)60753-8 In REF2*
3. Ewer AK, Furmston AT, Middleton LJ, Deeks JJ, Daniels JP, Pattison HM et al. Pulse oximetry as a screening test for congenital heart defects in newborn infants: a test accuracy study with evaluation of acceptability and cost-effectiveness. Health Technol Assess 2012; 16(2):1-184. *doi: 10.3310/hta16020 In REF2*
4. Roberts TE, BartonP, Auguste P, Middleton LJ, Furmston AT, Ewer AK. Pulse oximetry as a screening test for congenital heart disease in newborn infants: a cost effectiveness analysis. Archives of Disease in Childhood 2012 ; 97(3) : 221-226. *doi:10.1136/archdischild-2011-300564 In REF2*
5. Thangaratinam S, Brown K, Zamora J, Khan KS, EwerAK. Pulse oximetry screening for critical congenital heart defects (CCHD) in asymptomatic newborns: A systematic review and meta-analysis involving 229 421 babies. Lancet 2012 ; 379 (9835): 2459-2464 *DOI 10.1016/S0140-6736(12)60107-X In REF 2*
6. Powell R, Pattison HM, Bhoyar A, Furmston AT, Middleton LJ, Daniels JP et al. Pulse oximetry as a screening test for congenital heart defects in newborn infants: An evaluation of acceptability to mothers. Archives of Disease in Childhood 2013;98:F59-63. *DOI 10.1136/fetalneonatal-2011-301225*

4. Details of the impact (indicative maximum 750 words)

Critical congenital heart defects are an extremely serious issue for newborns, affecting around 1600 cases annually in the UK alone. Up to one third of these are not detected in basic hospital screening practices, and these babies are at significant risk of serious health complications and death. Through a portfolio of interlinked clinical and theoretical studies, Dr Ewer's work has provided extensive evidence of the clear benefits of pulse oximetry screening, and this has had major impacts on international policy and practice, as well as directly for children and their parents where the test has been implemented as a result. This research was described in a Lancet editorial as 'a new milestone in the history of congenital heart disease' [1].

Impact on international policy

The Lancet paper (2011) and subsequent HTA report (2012) received considerable international media attention and Dr Ewer has subsequently been invited to advise international policy makers considering the implementation of PulseOx screening.

- In 2011 Dr Ewer was invited as advisor to a working group of the Secretary's Advisory Committee on Heritable Diseases in Newborns' and Children (SACHDNC) in Washington, USA. Following this meeting the group advocated the introduction of pulse oximetry screening, endorsed by the American Academy of Paediatrics, American Heart Association and American College of Cardiology [2]. As a direct result, the US Secretary for Health and Human Services recommended the addition of pulse oximetry screening for CCHD across the US [3]. Thesenior cardiologist leading the SACHDNC group described Dr Ewer's study as having better design, appropriate reference and clarity of cardiac defect definition which meant that *'his data were instrumental in creating [the] recommendations'* [4], and that his work *"tipped the balance of evidence towards universal screening in the U.S.A"* [5].

- Dr Ewer recently advised Michigan State, and 7 states in the US are currently performing routine screening. The majority of states are making progress towards universal screening [6]
- Following a keynote lecture by Dr Ewer in Sydney, Australia, a state-wide PulseOx screening policy is being developed.
- Dr Ewer is currently advising Leiden University Medical Centre on a pilot study to assess the feasibility of implementing the pulse oximetry screening in the Netherlands
- Following a workshop on pulse oximetry screening in Beijing China in April 2013, including key representatives of Chinese national and regional screening committees, the President of the Children's Hospital of Fudan University, wrote to highlight that Dr Ewer's *"own advocacy role has been crucial in convincing my organisation of the importance of this technique in identifying cardiac defects and saving lives",* and that based on his work *"my team has been working on a similar screening project… which is showing encouraging outcome for those newborn babies with severe congenital heart diseases".*[7]
- The Vice-President of both Union of European Neonatal & Perinatal Societies and the World Association of Perinatal Medicine commented that Dr Ewer's work *"has been fundamental in prompting hospitals and policymakers internationally to consider adoption of this technique into routine clinical practice"*. He also noted on behalf of the Spanish Society of Neonatology that Dr Ewer's role has been *"crucial in preparing the proposal of a national neonatal screening recommendation… Our ongoing dialogue has already resulted in preparing a national guideline for Congenital Cardiac Disease Screening programme."*[8]
- The research was described in 2012 by the Irish Health Service Executive and Royal College of Physicians in Ireland as seminal research that "*should be undertaken in all Units across the country"*, as it was at that time only used in 6 of the 19 units [9]

Impact on UK practice and policymakers

In 2010 a national survey found that only 7% of UK neonatal units undertook routine pulse oximetry screening. A survey of 204 units in 2012 [10] indicated significant improvement, with almost 20% of units now utilising pulse oximetry routinely. In units which were not screening, 70% were actively considering it, clearly indicating a nationwide shift of opinion among UK neonatologists about pulse oximetry screening in their local units, with a substantial majority now in favour.

Birmingham Women's Hospital adopted pulse oximetry screening under the guidance of Dr Ewer. Over a 3 year period (2010-13) there were 187 admissions as a result of an abnormal screening test. This equates to approximately 60/year, just over one admission per week or 0.8% of all births. Of the 187 babies admitted 7 had a CCHD which had not been previously suspected. In addition, 5 other babies had a non-critical congenital heart defect which had not been suspected. Importantly, of the 180 babies which did not have critical congenital heart defects, many other serious health conditions (including congenital pneumonia, sepsis, and pulmonary hypertension) were identified as a result of pulse oximetry screening, and in fact only 36/180 (20%) of admitted babies had no serious health issues. This highlights important additional benefits for pulse oximetry screening beyond increasing identification of CCHDs.

Dr Ewer has also been actively involved in shifting opinion in the central decision-making unit for national screening programmes. The National Screening Committee (NSC) advises Ministers and the NHS in the UK on all aspects of screening, and supports implementation of screening programmes. Using research evidence, pilot programmes and economic evaluation, it assesses evidence for programmes against a set of internationally recognised criteria covering the condition, the test, the treatment options and the effectiveness and acceptability of the screening programme. Dr Ewer has been the key clinician involved in extensive discussions advising the Newborn and Infant Physical Examination (NIPE) programme within the NSC regarding possible implementation of pulse oximetry screening in the UK. This has resulted in a UK public consultation on 'Screening for Congenital Heart Defects', which highlights that *'There is now considerable research evidence to demonstrate that pulse oximetry… increases the detection rate of critical or life-threatening CHDs at the newborn screening opportunity'* and that *'Routine pulse oximetry is probably the most promising additional newborn screening modality'* under consideration, for which Dr Ewer's work provides the bulk of the underpinning evidence and rationale [11]. The Director, Population Health Science, Public Health England wrote in support of Dr Ewer's role in triggering the NSC debate

and further commented *"Without doubt the work that you led and the team research output has already led to considerable debate and change in the whole approach to ante natal and newborn screening, its value, culture and practice."*[12]

International campaign groups

A key ongoing impact of this work has been its use by lobbying groups, who have been very quick to recognise the benefits of pulse oximetry for screening newborns and are campaigning for its routine use in national practice. These groups all cite Dr Ewer's PulseOx study as the most important piece of evidence for their campaigns, and many national charities such as the Children's Heart Foundation, Little Hearts Matter, and Tiny Tickers have outlined their gratitude for the credence that Dr Ewer's work has given to their lobbying efforts with NIPE and collaboration with other congenital heart charities. In particular, the Children's Heart Foundation have provided a letter of support stating that:*"The extensive and compelling research from Dr Ewer into the effectiveness of Pulse Oximetry testing in detecting congenital cardiac conditions has been crucial to our understanding and work around the issue. It has allowed us to strongly make the case that this test should be introduced for newborns in the UK."*[13]

Internationally, campaign groups also commonly recognise the value of Dr Ewer's work, including http://pulseoxadvocacy.com/research/,a US site to support parents to lobby for the use of pulse oximetry, which cites the PulseOx study as one of "the most compelling pieces of evidence" that "should be part of any advocacy work".

5. Sources to corroborate the impact (indicative maximum of 10 references)

1. A new milestone in the history of congenital heart disease. Lancet. 2012 Jun 30;379(9835):2401. *doi: 10.1016/S0140-6736(12)61045-9. PMID: 22748572*
2. Kemper AR, et al. Strategies for Implementing Screening for Critical Congenital Heart Disease Pediatrics 2011:128:e1259-e1267 http://pediatrics.aappublications.org/content/128/5/e1259.full
3. U.S. Health & Human Services Makes Critical Congenital Heart Defect Screening Using Motion-Tolerant Pulse Oximetry a Nationwide Newborn Screening Standard. *PR Newswire* 23 September 2011.
4. Sensitivity of pulse oximetry for detection of critical congenital heart defects in newborn infants higher than that of antenatal ultrasound with few false positives. Martin GR, Bradshaw EA. Evid Based Med. 2012 Apr;17(2):57-8. *doi: 10.1136/ebmed-2011-100290*. Epub 2011 Nov 28.
5. Letter of support from the Senior Vice President Center for Heart, Lung and Kidney Disease, Children's National Medical Center.
6. Screening Map: http://cchdscreeningmap.org/
7. Letter of support from President of Children's Hospital of Fudan University
8. Letter of support from Vice-President World Association of Perinatal Medicine
9. Health Services Executive, Royal College of Physicians in Ireland. Pulse oximetry testing for newborn congenital heart disease. 2011
10. Singh A, Ewer AK. Pulse oximetry screening for critical congenital heart defects: a UK national survey. Lancet 2013;381:535. *doi:10.1016/S0140-6736(13)60278-0*
11. Screening for Congenital Heart Defects, External review against programme appraisal criteria for the UK NSC. September 2013http://www.screening.nhs.uk/congenitalheartdisease
12. Letter of support from Director of Population Health Science, Public Health England.
13. Letter of support from Children's Heart Foundation