Availability of active therapeutic hypothermia at birth for neonatal hypoxic ischaemic encephalopathy: A UK population study from 2011 to 2018

Authors: Dr Aarti Mistry[1], Dr Lara Shipley[1], Dr Shalini Ojha[1], Professor Don Sharkey[1,2] and the UK Neonatal Transport Research Collaborative (UK-NTRC)[2]

Corresponding Author: Professor Don Sharkey, Centre for Perinatal Research (CePR), School of Medicine, E floor, East Block, University Hospital, Derby Rd, Nottingham, NG7 2UH, UK. Don.Sharkey@nottingham.ac.uk. Tel no. 44 1158230611.

Affiliation 1: Centre for Perinatal Research (CePR), School of Medicine, University of Nottingham

Affiliation 2: UK Neonatal Transport Research Collaborative (UK-NTRC)

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Abstract:

Objective

Therapeutic hypothermia (TH) commenced soon after birth for neonatal hypoxic ischaemic encephalopathy (HIE) improves survival and reduces neurodisability. Availability of active TH at the place of birth (Immediate-TH) in the UK is unknown.

Design

Population-based observational study.

Setting

UK maternity centres.

Patients

5,975,056 births from 2011-2018.

Intervention Methods

For each maternity centre, the year active Immediate-TH was available and the annual birth rates were established. Admission temperatures of infants with HIE transferred from non-tertiary centres with and without Immediate-TH were compared.

Main outcome Measures

Quantify the annual number of births with access to Immediate-TH. Secondary outcomes included temporal changes in Immediate-TH and admission temperatures for infants requiring transfer to tertiary centres.

Results

In UK maternity centres, 75 of 194 (38.7%) provided Immediate-TH in 2011 rising to 95 of 192 (49.5%, P=0.003) in 2018 with marked regional variations. In 2011, 394,842 (51.2%) of 771,176 births had no access to Immediate-TH compared with 276,258 (39.3%) of 702,794 births in 2018 (P<0.001). More infants with HIE arrived in the therapeutic temperature range (76.5% vs 67.3%; OR 1.58, 95%CI 1.25-2.0, P<0.001) with less overcooling (10.6% vs 14.3%; OR 0.71, 95%CI 0.51-0.98, p=0.036) from centres with Immediate-TH compared to those without.

Conclusions

Availability of active Immediate-TH has slowly increased although many newborns still have no access and rely on transport team arrival to commence active TH. This is associated with delayed optimal hypothermic management. Provision of Immediate-TH across all units, with appropriate training and support, could improve care of infants with HIE.

“What is already known on this topic”

- Active therapeutic hypothermia (TH) for neonatal hypoxic ischaemic encephalopathy (HIE) improves survival without neurodisability
- Infants with HIE achieving early therapeutic target temperature are less likely to have seizures and a poor neurological outcome

“**What this study adds**”

- Between 2011 to 2018 in the UK, births with access to active TH in their birthing centre has marginally increased and marked regional variability exists

- In 2018, 39% of UK births did not have immediate access to active TH but almost all of these infants had access once the transport team arrived

“How this study might affect research, practice or policy”

- Increasing access to active TH in all birthing centres could improve the care infants with HIE receive and reduce current disparities

Introduction

Globally, hypoxic ischemic encephalopathy (HIE) is the largest contributor of term newborn brain injury with a UK incidence of 2.03 per 1000 live births for moderate/severe HIE (1), and is associated with significant costs from both a litigation and healthcare provision perspective (2). Therapeutic hypothermia (TH) is a well-established, safe and effective treatment for HIE if commenced within six hours of birth (3), increasing survival without disability (4, 5). In the UK, initiatives are underway to halve birth-related brain injury by 2025 (6, 7).

The diagnostic criteria used to commence TH in the TOBY trial (8) have been widely adopted including in UK national guidance (9). These criteria include early identification of risk factors and neurological status supported with amplitude-integrated electroencephalography (aEEG), which has become a useful tool in the management of HIE and supporting outcome prediction (10). Active TH using a servo-controlled device provides the optimal method of administrating targeted hypothermia in a controlled way (11). These devices are more effective in reaching and maintaining optimal therapeutic temperatures of 33-34°C (8, 9) compared to passive cooling where the risk of overcooling (<33°C) and potential harm is greater (12, 13).

In the UK, active TH was primarily adopted by neonatal intensive care units i.e., tertiary cooling centres; its recognition of benefit and the technology's relative simplicity and safety has led to uptake by other maternity centres and transport teams (14-16). Both animal and human studies suggest that the earlier the target temperature is achieved the better the neurological outcome (17-20), hence access to active TH in all maternity centres should be considered to ensure equitable provision (21).

Study aims

The aim of the study was to quantify the proportion of births in the UK who have access to active TH in their birth centre (Immediate-TH) and identify any temporal changes and regional disparities. In addition, we aimed to compare the temperature on admission to a tertiary cooling centre for infants with HIE following transfer from non-tertiary centres with and without Immediate-TH.

Methods

Access to TH equipment

UK maternity centres with access to active TH between 2011 and 2018 were identified in two ways. First, using the TOBY register (8) of UK cooling centres we identified those undertaking TH in 2011. Second, members of the UK-Neonatal Transport Research Collaborative (UK-NTRC) completed a survey identifying each maternity centre within their neonatal network with access to active TH and the year commissioned. The availability of aEEG was also established at the end of 2018 to allow population coverage costs to be estimated. Each UK-NTRC transport service also identified the year they started active TH during transfer for infants with HIE. This allowed every maternity centre, by year, to be assigned one of three classifications:

1. Active TH available immediately at birth centre (Immediate-TH)
2. Active TH initiated on arrival of the transport team (Transport-TH)
3. Active TH initiated on arrival at a tertiary cooling centre (Tertiary-TH)

In the UK, tertiary centres are those providing neonatal intensive care (level 3), non-tertiary centres are local neonatal units (level 2) and special care units (level 1) who do not routinely care of infants with HIE requiring TH. For the purposes of the analysis, active TH did not include passive cooling.

Maternity centre births and neonatal units

Total births from 2011 to 2018 (the latest year data were available) were obtained for each maternity centre using national databases in England (NHS Maternity Statistics) (22), Scotland (Scottish Morbidity Register) (23), Wales (National Community Child Health Database and NHS Wales Informatics Service) (24) and Northern Ireland (Northern Ireland Statistics and

Research Agency) (25) (Supplementary Table 1). Births in England were reported as a maternity, each maternity counting as one birth (live and stillbirths) irrespective of the plurality (Supplementary Table 2). Where centres in England reported combined birth numbers within a healthcare Trust, their births were differentiated using a ratio of each centre's known birth rate obtained from the Office for National Statistics (26). Births in Scotland and Wales were reported as total births (live and stillbirths), Northern Ireland births were reported as live births. Freestanding midwifery-led centres were excluded, as they lack access to immediate neonatal care and TH initiation is not recommended from this setting (21), they account for <2% of the total UK births (27, 28).

Modelling ambulance journey times

For maternity centres without Immediate-TH, road journey times were calculated between the transport service base to referring maternity centre and then to their nearest tertiary cooling centre using online mapping software (29). Mean journey times were calculated from three estimated hypothetical journeys over a range of time points (midweek morning, weekday afternoon, weekend morning). Initiating TH for HIE within six hours of age is a benchmark agreed by neonatal transport services internationally (30), although HIE is not universally considered time critical (30-32). As a proxy for timely despatch, a 60-minute despatch time was added to each journey to represent the quickest time critical turnaround time. These journey times were used to model estimates for the earliest potential time that active TH could be commenced from the point of referral to a transport service (The Isle Wight centre was excluded as it combines road and sea transfer).

Clinical database

Using data from a parallel study (1), infants 36 to 42 weeks' gestational age, born in a UK non-tertiary centre between 2011 and 2016, with a diagnosis of moderate/severe HIE and were transferred for TH were identified from the National Neonatal Research Database (NNRD) (33). Admission temperature following transfer to the tertiary cooling centre was compared between birth centres with and without Immediate-TH, using specific NNRD data fields (Supplementary Table 3). The NNRD collates prospective demographic and clinical data, which is anonymised and cleaned by the Neonatal Data Analysis Unit prior to its entry into the database. The NNRD is a designated approved dataset outlined by the National Neonatal Data Set and validated by the Standardised Committee for Care Information (33, 34).

Statistical Analysis

Descriptive statistics were used to describe the provision of Immediate-TH, Transport-TH and Tertiary-TH for each year and chi squared test for trend (Cochran-Armitage test) used to assess significance of trends over time. Collating each centres data into neonatal networks (35) identified regional variations. Ambulance journey times for each year were tested for normality and Kruskal-Wallis with Dunn's correction used to assess significance. Secondary outcomes were described using odds ratio (OR) and chi squared for trends. A p value <0.05 was considered statistically significant. All analyses were performed in GraphPad Prism 9.

Results

From 2011 to 2018, there were a total of 5,975,056 births included in the analysis. The total births across the UK declined by 9% from 2011 to 2018 (Supplemental Table 4).

Access to active TH

In 2011, there were 194 maternity centres with 75 (38.7%) providing Immediate-TH, increasing in 2018 to 95 of 192 centres (49.5%, p=0.003, Table 1). Expansion of Immediate-TH mostly occurred in local neonatal units. Proportionally, births with Immediate-TH access increased from 376,334 (48.8%) in 2011 to 426,536 (60.7%) in 2018 (p<0.001, Supplementary Table 4).

Of the 394,842 (51.2.%) births occurring in centres without Immediate-TH access in 2011, 171,775 (43.5%) had access to Transport-TH with 223,067 (56.5%) reliant on transfer for Tertiary-TH. In 2018, the number of births without access to Immediate-TH was 276,258 (39.3%) with significantly more able to access Transport-TH (273,382, 98.9%) compared to 2011 (p<0.001, Supplemental Table 4). By 2016, over 99% of births had access to either Immediate-TH or Transport-TH (Figure 1). By 2019, the UK-NTRC reported 129 of 192 maternity centres had aEEG equipment.

Regional differences

The median percentage of births in regions with Immediate-TH was 52.6% in 2011 and 64.9% in 2018 (Supplemental Table 4). Over the study period, only 8 of 14 networks increased the number of maternity centres with Immediate-TH provision. The South East Coast Neonatal Network had the greatest increase in the percentage of births with Immediate-TH from 32.2% in 2011 to 95.4% in 2018 (Figure 2).

Earliest potential time to commence active TH

In the UK, neonatal transport services underwent reconfiguration reducing from 20 to 15 transport services over the study period. By 2017, 14 of the 15 transport services provided active TH in transit for infants with HIE. For maternity centres without Immediate-TH, the earliest potential time to start active TH by either Transport/Tertiary-TH from the point of referral was estimated (Figure 3). In 2011, those without Immediate-TH had a median time of 122 minutes (IQR 105-146), with maximum time of 328 minutes to commence active TH; by 2018, the median time reduced to 104 minutes (IQR 92-129, P<0.001), with maximum time of 243 minutes.

Admission temperatures

Between 2011 to 2016, 2,573 infants were born in non-tertiary centres with moderate/severe HIE and were transferred to a tertiary cooling centre for TH. Of these infants, 475 (18.5%) had access to Immediate-TH and the remaining 2,098 (81.5%) required Transport-TH or Tertiary-TH (Supplementary Table 5). 2,466 infants had admission temperatures recorded following transfer (Supplementary Table 6). In 2011, there was no difference between infants achieving optimal therapeutic temperatures (33-34^{o}C) with or without Immediate-TH (64.3% vs 60.4% respectively; OR 1.18, 95%CI 0.61-2.25, p=0.63, Figure 4). In 2016, infants with Immediate-TH were more likely to arrive within therapeutic range (83.5% vs 73.7%; OR 1.81, 95%CI 1.05-3.16, p<0.036, Figure 4). Overall, infants without Immediate-TH (n=2,011), compared with Immediate-TH (n=455), were more likely to arrive outside the optimal therapeutic temperature range (32.7% vs 23.5%; OR 1.58, 95%CI 1.25-2.0, p<0.001) and have an admission temperature <33^{o}C (14.3% vs 10.5%; OR 1.41, 95%CI 1.02-1.95, p=0.036, Supplementary Table 6).

Discussion

Neonatal HIE is the leading cause of brain injury in term infants and treatment within six hours of birth reduces death and disability (4, 5), with some evidence the earlier therapeutic temperature is reached the better the outcome (17, 19, 20). This is the first national study to describe the temporal changes and regional variations in access to active Immediate-TH in maternity centres. During the study period there has been a small increase in availability of TH, mostly in local neonatal units, with 50,000 more births in 2018 having access to Immediate-TH if needed. Despite this, approximately 275,000 (39%) of UK births in 2018 still occurred in centres without Immediate-TH.

Using six years' worth of national data, we identified 2,098 infants with HIE who were transferred to a tertiary cooling centre from a maternity centre without Immediate-TH. This equates to approximately 350 babies per year who potentially receive suboptimal TH with passive cooling. The delay achieving therapeutic temperatures and the risk of overcooling may adversely impact their outcome (12, 13). The adoption of active TH by neonatal transport teams has partly compensated this, with over 98% of births without Immediate-TH now able to access TH at their birth centre on the arrival of the transport team. Infants with HIE born in centres with active TH were more likely to be in the therapeutic temperature range following transfer to the tertiary centre (36) and, importantly, less were overcooled which is associated with adverse effects (12, 13).

We observed inequalities in UK availability of Immediate-TH with access varying from 31-95% of regional network births. The significant improvement in the South East Coast Network reflects work from their network-wide quality improvement project ‘Time=Brain’ consisting of education, outreach training and provision of TH equipment (37). To implement similar initiatives nationwide would require an estimated £2.5 million to provide active Immediate-TH and aEEG equipment for those centres without these resources. These costs seem small compared to the £1.9 billion incurred annually in the UK around litigation claims for birth-related brain-injury (2, 38), not including the additional healthcare expenses for disability (2). Based on this analysis, the current rate at which Immediate-TH provision is increasing, approximately 6,300 more births per year, it could take a further 40-years without additional resource for the remaining birth population to gain access.

Expansion of Transport-TH over the study period was linked with benchmarking and reporting by the UK-Neonatal Transport Group (UK-NTG) against national transport targets (32). In addition, neonatal transfer studies have found servo-controlled-TH to be safe and effective (14-16, 39). Consequently, there was a rapid increase in Transport-TH, effectively reducing the potential time to initiate active TH by almost two hours (10, 16).

Animal studies support early TH (<3 hours of age) with less neuronal loss and better neuroprotection compared with late (3-6 hours) or delayed (>6 hours) treatment (17, 18, 20, 40). This is supported by observational human data showing better motor development (19) and less occurrence of seizures (41, 42). Seizures associated with HIE can increase the long-term risk of a poor neurodevelopmental outcome (43-45). For some infants with HIE requiring transfer, achieving therapeutic temperatures within six hours of age, even with Transport-TH, is still challenging. The UK-NTG 2019 data reported only 76% of 279 infants with HIE transferred with active TH reached the therapeutic temperature target by six hours of age (31). We demonstrate nationally, more infants in non-tertiary centres with Immediate-TH achieve therapeutic temperatures, with less overcooling on arrival to their tertiary cooling centre than those without Immediate-TH. Similar benefits have been reported where infants reach therapeutic temperatures two hours earlier if active TH was commenced prior to the arrival of the transport team compared to infants passively cooled (13, 36). Access to Immediate-TH could help alleviate the time pressure faced by transport teams (30-32) and potentially improve outcomes for at risk infants, through early TH initiation, a recommendation incorporated into a new UK national framework (21).

Strengths and limitations

The strengths of this study include the utilisation of national data to quantify changes over time across an entire healthcare system in the UK. We also used nationally collected data on infants transferred for TH from non-tertiary centres providing insights into the temporal changes on temperature control.

The main limitation of our study is the birth denominators varied by country, potentially underestimating by 20-25,000 each year due to English births being reported as maternities, equating to approximately 3% of the population.

Additional limitations include the model estimates on the earliest potential time to start TH do not factor in real-time delays of road-traffic conditions, variable dispatch time or the age at which a referral is made (14, 31). The use of NNRD for HIE does have limitations (1) but the large cohort of infants analysed partly mitigates this. We have not adjusted for differing clinical variables which may influence temperature data. Additionally, varying practices between maternity centres and transport services could not be accounted for. Finally, we there could be recall bias with healthcare professionals identifying the year TH was commissioned.

Conclusion

Availability of Immediate-TH for HIE has gradually increased across maternity centres in the UK, however, there remains significant variability between regions resulting in disparities with access to optimal care. To reduce birth-related brain injury and implement new UK frameworks, investment is needed now to expand the provision of active TH and aEEG to all maternity centres, alongside training, education and support by tertiary centres. This cost-effective solution could address the inequalities in delivery of TH, alleviate pressures on transport teams and help improve outcomes through earlier initiation of TH.

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Electronic patient data recorded at participating neonatal units that collectively form the United Kingdom Neonatal Collaborative (UKNC) are transmitted to the Neonatal Data Analysis Unit (NDAU) to form the National Neonatal Research Database (NNRD). Don Sharkey had full access to all the data in the study and takes full responsibility for the integrity of the data and accuracy of the data analysis. We are grateful to all the families that agreed to the inclusion of their baby's data in the NNRD, the health professionals who recorded data and the NDAU team.

Author contributions

AM and DS made substantial contributions to the concept, planning, design of the study and acquisition of data. LS and DS collated the secondary outcome data from the NNRD. The UK-NTRC helped identify centre equipment access and revised the final manuscript. AM, LS, SO and DS assisted in drafting and editing the manuscript. All authors approved the final version for publication.

Collaborators

On behalf of the UK-NTRC an affiliated group of the UK-NTG: E Adams, I M Dady, H Darby S J Davidson, N Davey, N Fowler, C H Harrison, A Jackson, J Madar, A Leslie, S Pattnayak, A Philpott, N Ratnavel, S Rattigan, J Tooley, P Turton, M S Reddy, P Sakhuja, R Tinnion, A Walker and L Watts. Collaborators affiliations respectively: Oxford University Hospitals NHS Foundation Trust; Connect North West Neonatal Transport Service, Manchester University NHS Foundation; University Hospitals Plymouth NHS Trust, Plymouth, UK; University Hospitals Southampton NHS Foundation Trust; CenTre Neonatal Transport Service,

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Competing interests

No conflicts of interest to declare.

Ethical approval

The study was performed in line with the principles of the Declaration of Helsinki. Ethical approval was granted by London – City and East Research Ethics Committee (REC: 17/LO/1822).

Data availability statement

All National Birth statistics were obtained from publicly available databases. All survey data from UK-NTRC was contributed freely and under consent of each UK Neonatal Transport service. NNRD data extracted and supplied by the Neonatal Data Analysis (NDAU) were available from the corresponding author on reasonable request and with permission of the study team and NDAU.

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Table 1 UK maternity centres and neonatal units with provision of therapeutic hypothermia (TH) from 2011 to 2018

Year	2011	2012	2013	2014	2015	2016	2017	2018
Number of UK maternity centres	194	195	195	194	194	193	193	192
Immediate-TH, n (%)	75 (38.7)	77 (39.5)	78 (40.0)	80 (41.2)	85 (43.3)	87 (45.1)	93 (48.2)	95* (49.5)
Transport-TH, n (%)	52 (26.8)	63 (32.3)	81 (41.5)	80 (41.2)	105 (54.1)	103 (53.4)	98 (50.8)	95** (49.5)
Tertiary-TH, n (%)	67 (34.5)	55 (28.2)	36 (18.5)	34 (17.6)	11 (5.7)	3 (1.6)	2 (1.0)	2 (1.0)
Neonatal units with Immediate-TH								
NICU (Level 3), n (%) [a]	53 (92.9)	55 (96.4)	55 (96.4)	56 (98.2)	56 (98.2)	56 (98.2)	56 (98.2)	55 (98.2)
LNU (Level 2), n (%) [a]	22 (24.2)	22 (24.4)	23 (25.3)	24 (26.4)	24 (31.9)	31 (34.1)	32 (35.2)	35 (38.5)
SCU (Level 1), n (%) [a]	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	5 (11.1)	5 (11.1)

NICU=Neonatal Intensive Care Unit; LNU=Local Neonatal Unit; SCU=Special Care Unit; *p=0.003 and **p<0.001 Chi squared test for trend.

a=Percentage based on total number of units with each level

Figure 1. Provision of Immediate-TH, Transport-TH and Tertiary-TH in relation to percentage of total UK births from 2011 to 2018. ** p<0.001 Chi squared for trend Immediate-TH compared to those without Immediate-TH.

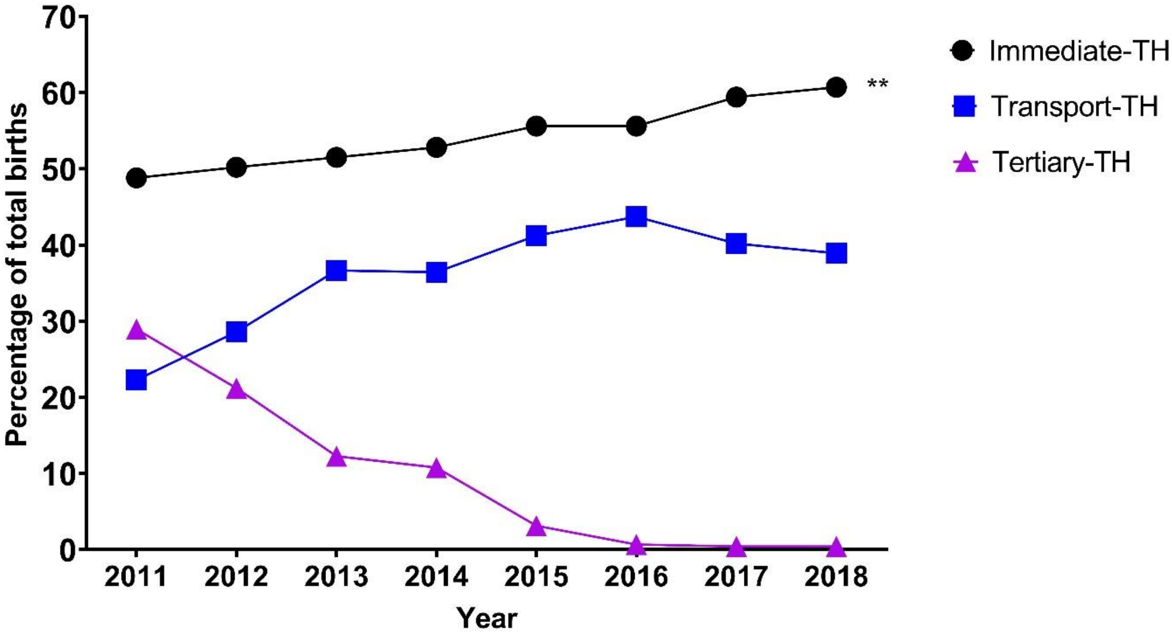

Figure 2. Heat Map showing the percentage of births within UK regions, based on neonatal networks, with Immediate-TH access in 2011 and 2018. The scale is presented as quintiles of the percentage of regional births with Immediate-TH access. Powered by Bing © DSAT for MSFT, Geonames, Microsoft, Navteq.

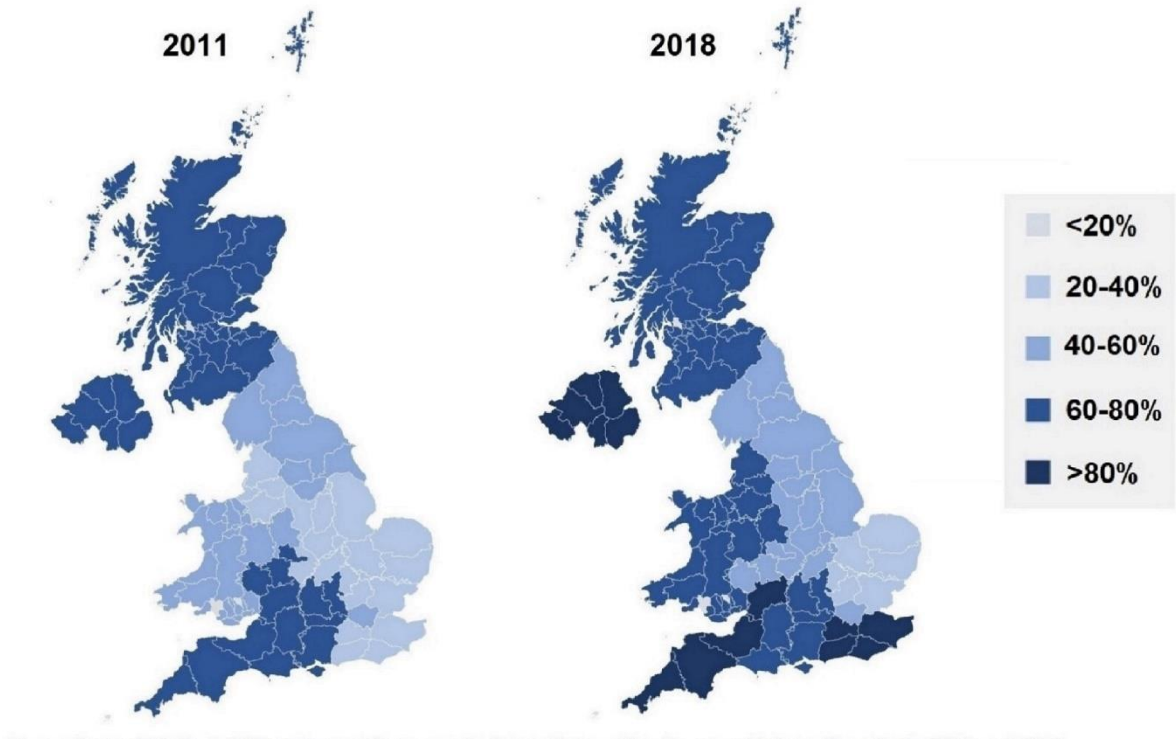

Figure 3. Violin plot of earliest estimated time to start active TH from the point of referral for births in centres without Immediate-TH from 2011-2018. Statistical significance comparing 2011 to 2018 using Kruskal-Wallis and Dunn's correction test, ** p<0.001.

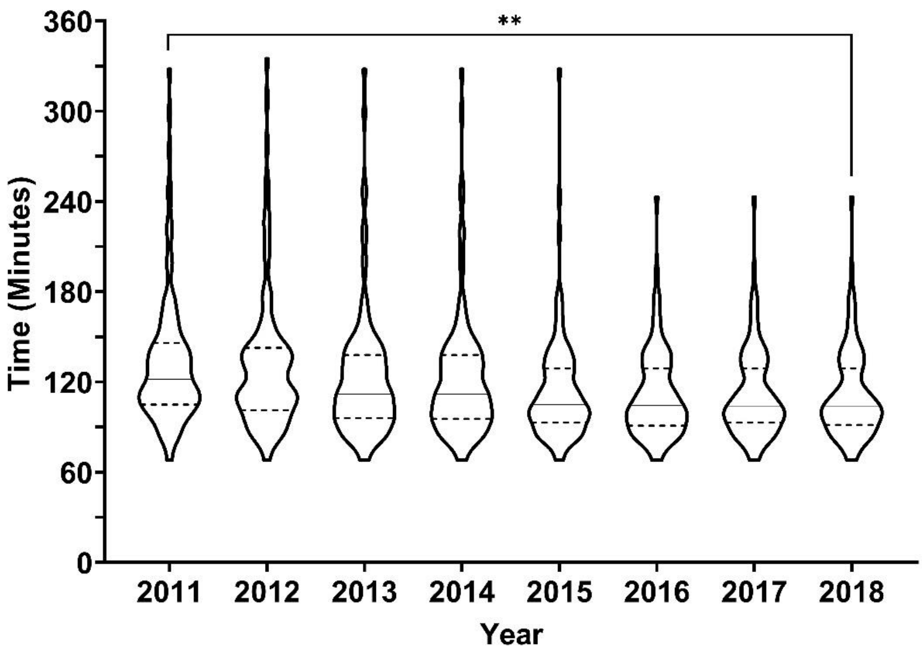

Figure 4 The percentage distribution of admission temperatures on arrival to the tertiary cooling centre of infants ≥36 weeks gestational age with moderate or severe HIE born in non-tertiary centres without Immediate-TH (n=2011, Figure 4a) and with Immediate-TH (n=455, Figure 4b) from 2011 to 2016. Chi squared for trend for temperature within therapeutic range (33-34°C), Infants without Immediate-TH, $p < 0.001$ and infants with Immediate-TH $p<0.01$.