Review Article

Economic assessment of neonatal intensive care

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Abstract: Most of the studies on the costing of neonatal intensive care has concentrated on the costs associated with preterm infants which takes up more than half of neonatal intensive care unit (NICU) costs. The focus has been on determining the cost-effectiveness of extreme preterm infants and those at threshold of viability. While the costs of care have an inverse relationship with gestational age (GA) and the lifetime medical costs of the extreme preterm can be as high as $450,000, the total NICU expenditure are skewed towards the care of moderate and late preterm infants who form the main bulk of patients. Neonatal intensive care, has been found to be very cost-effective at $1,000 per term infant per QALY and $9,100 for extreme preterm survivor per QALY. For low and LMIC, where NICU resources are limited, the costs of NICU care is lower largely due to a patient profile of more term and preterm of greater GAs and correspondingly less intensity of care. Public health measures, neonatal resuscitation training, empowerment of nurses to do resuscitation, increasing the accessibility to essential newborn care are recommended cheaper cost-effective measures to reduce neonatal mortality in countries with high neonatal mortality rate, whilst upgraded neonatal intensive care services are needed to further reduce neonatal mortality rate once below 15 per 1,000 livebirths. Economic evaluation of neonatal intensive care should also include post discharge costs which mainly fall on the health, social and educational sectors. Strategies to reduce neonatal intensive care costs could include more widespread implementation of cost-effective methods of improving neonatal outcome and reducing neonatal morbidities, including access to antenatal care, perinatal interventions to delay preterm delivery wherever feasible, improving maternal health status and practising cost saving and effective neonatal intensive care treatment.

Keywords: Costs; cost-effectiveness; economic evaluation; neonatal intensive care unit (NICU); preterm

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Introduction

Neonatal intensive care (NIC), estimated at USD 26.2 billion a year in the United States (1,2) is expensive but known to be cost effective (3). With escalating health expenditure, resource allocation by the government or public sector will to a large extent be determined by health economic evaluations of new technologies or innovations.

Neonatal mortality rate is taken as an index of the health standard of the country and thus governments have been expected to provide for and promote health in newborns, in order to accomplish the Millennium Development Goals before 2015, and now to achieve the Sustainable Development Goals of preventing and caring for preterm birth. In low- and middle-income countries (LMIC), public health measures translate to saving more lives in countries which can ill afford the subsequent cost of prematurity or prolonged neonatal intensive care. Resource allocation for the NIC is currently limited in countries with high rates of preterm births and families bear the major burden of the NIC costs (4-6).

The objective of this article is to provide a review of the literature on economic evaluations of NIC, with an emphasis on low and middle income countries, from the perspectives of the payer who may be the public sector, families or society. From a broad perspective, these include costs or resources utilised that include both direct costs, such as initial hospital costs, those associated with health follow-up and care associated with morbidities from preterm complications, as well as indirect costs, from the societal perspective such as educational and rehabilitation costs and costs borne by the family.

Pooling of economic data is difficult because of methodological variations between studies, such as the use of charges versus cost or cost to charge ratio, the variability in the costing methods or the lack of detailing of costs, birth weight used by many studies as compared to gestational age (GA), the variable time periods covered by the studies, and the inclusion or lack of inclusion of social costs to families. Therefore, the studies are presented in a qualitative manner.

Costs were adjusted using purchasing power parity (PPP) of different currencies to USD at year 2016, unless otherwise stated. The tool CCEMG – EPPI-Centre Cost Converter (7) utilised historical conversion rates and 'Implied Purchasing Power Parity conversion rate' dataset, obtained from the IMF World Economic Outlook Database and allowed for price inflation conversion from the reference year to year 2016.

Neonatal intensive care costs of term babies

The cost for in-hospital per term infant averaged $2,500–2,900 (8-10) with mean duration of stay being 2.2 days (11) compared to $800 for an uncomplicated newborn (10). As such, most of the studies on NICU costs did not cover the detailed costs of term babies specifically but total in-hospital costs are found in the comparison with preterm costs. This would include costs for the common admissions for respiratory problems, neonatal encephalopathy, sepsis, intrauterine growth retardation and congenital anomalies.

A recent study by Helle *et al.* looked at the health care related costs of early term (37–38 weeks GA) infants within a population of 29,970 births in Finland (12). During the first 3 years of life, the costs at $3,910 per child in the early term group, were higher than for full term children at $3,300. The early term babies were more likely to have been delivered earlier for maternal or fetal indication and had increased morbidity costs due to obstructive airway diseases, ophthalmological, and motor problems, suggesting that early term infants are at a health disadvantage (12).

Follow-up costs were not available as term babies are generally healthy except for those with birth defects, syndromic babies, cerebral palsy and genetic conditions. Treatment of congenital anomalies in neonatal intensive care unit (NICU) are usually those requiring surgery in the neonatal period. The majority are critical congenital heart disease, neural tube defects, gastroschisis, and Down syndrome related. A comprehensive study by Waitzman *et al.* (13) gave the lifetime medical costs per case of birth defects from California cohort but the costs from familial perspective, indirect costs of loss of productivity, excess medical costs not covered by insurance and educational costs were not included in this study. These studies are largely focused on paediatric hospitalisation and overall national costs for chronic care, instead of NIC costs and shall not be addressed further beyond this section.

The cost of prematurity

Much of the literature on economic evaluation of NIC is focused on the preterm-associated costs. In a California population based study (14), very low birth-weight (VLBW) infants comprised 0.9% of the birth population but accounted for 37.5% of the total costs, whilst low birth-weight (LBW) infants accounted for 5.9% of admissions and 56.6% of total hospital costs for newborns. GA has been shown to be the strongest predictor of prematurity costs. There were mean cost savings of about $35,000–39,750 for every 1-week increase in GA at birth as demonstrated by Phibbs *et al.* on studying the hospital costs of a California-based cohort of 264,870 infants from 24 to 37 weeks gestation (9). All related studies produced an inverse relationship between GA at birth and costs related to hospital costs and long-term health services (15,16).

Soilly *et al.* (16) published a comprehensive review paper on the economic analysis of costs associated with prematurity in the year 2014—looking at a total of 18 papers published since 1990. Thirteen of the studies were from the USA, three were English, one Finnish and one Greek. There were marked variations in mean costs per category of GA. These factors were described in the paper as due to different payer perspectives, method of calculating costs such as some using cost-to-charge ratio methods, variable inclusion of indirect medical or social costs, or different duration of follow-up. In the short-term studies from birth to the first year of life, the costs for the most extreme preterm group, varied from $12,910 to $297,627, for very preterm $11,640 to $149,101, for moderate prematurity from $7,200 to $46,117 and for late prematurity from $2,362 to $7,870 (unadjusted for year). Despite the variations, the average weighted mean costs of four similar short term studies for those less than 28 weeks gestation at birth were at over $100,000, those of 28 to 31 weeks GA $40,000–100,000, those of 32 to 34 weeks GA $10,000–30,000 and for those of 35 to 36 weeks GA, the costs were under $4,500 (unadjusted for year). Mean initial hospitalisation costs for surviving preterm or low birth weight infants in 2001 sampled from a US National Information System, were not significantly different from non-survivors at $28,300 and $27,000 respectively but the median cost for deaths was much less at $2,800 compared to the median cost among survivors at $9,660 (10).

Extreme preterm comprise 6% of preterm populations but takes up one-third of medical costs for preterm birth up to 7 years of age. The hospital cost per survivor at 25 weeks gestation was found to be $292,000 and $124,000 at 28 weeks (17). From Petrou's review of the literature since the 1970's, hospital costs for ELBW infants were 75% higher than the infants 1,000 to 1,499 gm, related to longer days of assisted ventilation, and increased costs from surgical interventions (18).

Despite the higher costs with the extreme preterm group, total program costs for NIC are derived mainly from the costs for the larger preterm infants, as 85% of preterm births being admitted to NICU are occurring at or after 32 weeks gestation (16,19,20). In addition, infants born between 32–36 weeks gestation had a 3.3-fold increase in 5-year hospital service costs compared to term infants from a study of hospitalisation costs of nearly 240,000 infants born in Oxfordshire and West Berkshire during 1970–1993 (18). On that same finding, Gilbert *et al.* demonstrated that the costs of NIC in 1996 for each GA group was $38 million and that cost-savings could potentially be higher by reducing the number of infants delivered between 34–37 weeks GA, rather than withholding NICU care for the extreme preterm infants (17). Mohan and Jain (21) had advocated for strategies to reduce the number of late preterm infants for which the obstetric indications for preterm delivery were not clearly warranted.

Economic costs of neonatal intensive care should also take into account costs to the families. This would include parent's loss of earnings, travel, child care for siblings and any specialised home care for the patient (22). Tommiska *et al.*'s study in Finland (23) valued mean direct non-medical costs and lost productivity before discharge of parents of extremely low birthweight infants at $4,730 or 4% of total costs. The costs to the family were mainly from travel costs which constituted 64%, with the remainder attributed to lost earnings (30%) and family accommodation costs (6%). An earlier study from the UK reported similarly that travel costs was the main expense with a median total expenditure of $265–530 (24). Family income subsequent to a preterm birth has also been found to drop by 20–32% in the United Kingdom (25).

Asian studies on cost of NICU

There are relatively few studies on the economic costs of NIC in Asian countries. Some of these studies conducted may have been in languages other than English. All available were presented as costs according to infant birth weight groups instead of GAs, and that may be due to birth weight data being more reliable than GA estimation and documentation. There were methodological differences in the costing compared to that in developed countries, the range of patients and treatment given as well as major cost differences in the cost and amount of consumables used with different technologies, hospital fees and emolument of staff. The large difference in price between these countries and developed countries is probably related to the much higher staff emolument, better survival rate and therefore longer length of stay and intensity of care, possibly less preterm complications for the larger preterm in the developed countries.

Narang *et al.* (26) studying neonatal admissions to a Indian tertiary referral teaching hospital found that the cost per hospital admission was $4,950 for 500–999 gm birth weight, $2,600 for 1,000–1,249 gm, $1,240 for 1,250–1,499 gm, $850 for those 1,500–1,749 gm and $620 for those above or equal to 1,750 gm birth weight. Costs borne by families ranged from $520 per hospital admission for those infants above 1,750 gm to $4,500 per infant from 500–999 gm birth weight. The costs included duration of stay in the special care nursery and NICU stay was much shorter. Sixty-six percent of the patients were term infants and only 1.1% were below 28 weeks GA. Overall survival rate was not mentioned in the study (26). The median cost of neonatal care in a private NICU was reported as $275 (27). Only 7.1% of the 126 neonates studied were below 1,500 gm birth weight and 36.5% of birthweight between 1,500 to 2,000 gm. Intensive therapy was required for about 25% of the patients. The India National Action Plan (INAP) launched in 2014 has resulted in the set-up of facility based newborn care at different levels, delivering essential newborn health care, newborn stabilisation units and special care neonatal units. The estimated amount to cover the costs of all SCNUs is INR40 billion (almost $3 million), but would be only 0.8% of the Indian national health expenditure (28).

In Pakistan, the NICU in a tertiary referral centre described an overall 20% mortality rate in the year 2007 with more than 200% bed occupancy rate. Average cost per admission was only $1,530. NICU admissions included term infants in the NICU whilst the cost for preterm infants who were mainly more than 30 weeks gestation was $115 per day. The mean length of stay was 4.7 days for both survivors and non-survivors. In contrast to other studies, the non-survivors required more consumables so not unexpectedly the costs of non-survivors were higher in this study (29). The costs, although seemingly low, is non-comparable with the other studies in view of the different patient population and treatment given. However, the paper reflects the situational context of the resources available for newborn infants who required NIC in Lahore, Pakistan in the year 2007.

The costs for the Indian studies were lower than in a Malaysian study (30) whereby the cost per hospital admission in 1999 for the infants between 1,000–1,499 gm was $4,610. Narang *et al.*'s study from India had a higher percentage of infants above 32 weeks gestation, 90%, as compared to 40% of infants above 31 weeks in the Malaysian study of five tertiary hospitals. Most NICUs in Malaysia were not all aggressively managing ELBWs in 1999. In view of the relatively low costs, it was found to be cost effective for the birth weight category 1,000–1,499 gm. The survival rate for infants of that birthweight category in Malaysia in 1999 was 78% which has increased to 89% in the year 2017 (unpublished data from Malaysian National Neonatal Registry). Government hospitals in Malaysia presently bear the major part of preterm birth costs, whilst private neonatal intensive care costs are borne by private health insurance and less commonly by the families.

Liao's paper discussed the overall Chinese government's overall investment for newborn care in the years 2008–2010 to be of $100 million, with a median yearly investment of $377,500 to a single newborn unit, primarily for the purchase of medical equipment, scientific research, personnel training, and newborn ward reconstruction (31). The daily hospital cost for an ELBW infant was $188, hospital cost of the average length of stay of about 49 days was $9,432 as found in five hospitals in four metropolitan cities. The lower cost compared to developed countries is attributed by the authors as due to insufficient health staff and difference in service quality and shorter duration of stay. Survival rate ELBW above 500 gm birth weight was 76% in the 5 hospitals where high quality health professionals, advanced equipment and research funding was concentrated (31), as compared to the average survival rate ELBW 41% and VLBW 82% in 109 hospitals in year 2009 in other parts of China (32). The NICU costs were three times that of per capita disposable income of local urban residents, and almost 63 times the per capita health expenditure in 2011 (31). Although 95% of households receive subsidised health insurance since 2011, half of the NICU costs, and all of the follow-up costs and care of disability have to be borne by the families (33). Not surprisingly, 56.3% of deaths in 26 tertiary hospitals in China were from medical withdrawal in accordance with parental wishes due to fear of poor prognosis and 46.2% to financial constraints (34).

There was only one readily available study with full text from Taiwan, in the English language. Hsieh *et al.* looked at the average total hospital costs for the NICU survivors from National Taiwan University Hospital between 01 January 1997 and 30 June 2004 with birthweight ≤500 g (35). The costs for these micro-preemies were US $52,750 and the average hospital cost per day was US $435. Financial constraints yet again tended to be the most important factor that influenced parental decision for comfort care despite the availability of health insurance in Taiwan.

Successful implementation of neonatal resuscitation practices are reported in China, whereby changes in policy permitted midwives to initiate resuscitation and conditions were imposed requiring newborn resuscitation training as part of their midwifery or nursing license. In his study, Xu *et al.* (36) described the decline in intrapartum-related deaths in the delivery room from 7.5 to 3.4 per 10,000 from years 2003 to 2008, and the incidence of Apgar ≤7 at 1 minute decreased from 6.3% to 2.9%, after more than 110,659 health care professionals were trained in NRP in 94% of delivery facilities in 20 targeted provinces in China.

Generally, with the high mortality rates in India and Pakistan of 24 and 44.2 per 1,000 livebirths (37), it was recommended that cheaper cost-effective measures on improving the delivery of early essential newborn care as a package with maternal healthcare was a priority, rather than to focus on NICU's and VLBW infants until such time when the neonatal mortality drops towards 15 per 1,000 livebirths (38,39). Saving extremely preterm neonates as well as long-term rehabilitation programs imposes high cost of care and treatment, which may not be a priority for health systems in developing countries. Health workforce competence and accessibility and quality of health service delivery, as well as health financing were major bottlenecks in the four interventional packages to reduce neonatal

Table 1 Recommended strategies for implementation in low- and middle-income countries to improve the survival of preterm infants (40,61)

Improving health workforce competence, accessibility and quality of perinatal health service delivery
Prophylactic maternal steroids in preterm labor
Antibiotics for premature rupture of membranes
Community case management of neonatal sepsis and pneumonia
Delayed cord clamping
Room air (*vs.* 100% oxygen) for resuscitation
Vitamin K supplementation at delivery
Hospital-based kangaroo mother care
Early breastfeeding
Thermal care immediately after birth—skin-to-skin contact and plastic wrap
Surfactant therapy and application of continued distending pressure to the lungs for respiratory distress syndrome

mortality in 2005 (40). These four interventional packages to reduce neonatal mortality in developing countries were prevention and management of preterm births including neonatal resuscitation, inpatient supportive care of ill and small newborn babies, the use of kangaroo mother care and the management of severe infections.

Costs of morbidities with prematurity

Economic assessments of NIC should necessarily take into account the long-term care of the surviving preterm with attendant complications. Russell *et al.* reported that mean hospital costs for preterm infants with common morbidities of prematurity are four to seven times higher than their GA equivalent healthy controls (10).

Directs hospital costs were increased by $13,500 with the presence of brain injury, $17,000 with necrotizing enterocolitis (NEC), $31,500 with bronchopulmonary dysplasia (BPD), and an increase of a $11,000 with late-onset sepsis, in a study of 425 VLBW infants in US from year 2005 to 2009 (41). Further detailing of the NEC cases showed an increase in direct medical costs of $24,750 in patients with surgical NEC versus $14,560 in patients with medical NEC. Other than the surgically related costs, increased length of stay, increased use of parental nutrition, as well as additional diagnostic and therapeutic interventions are incurred in infants with NEC compared to those without NEC. Other studies in the United States show a similar economic burden of NEC (42,43).

Russell *et al.* (10) reported that infants with BPD had an initial hospitalization cost that was six times higher than the cost of infants without BPD, median cost of $135,000 per infant compared to a median of $21,200. This compares to $48,700 for all infants less than 28 weeks' GA and $660 for uncomplicated newborns in this study. Studies elucidating costs associated with BPD were well reviewed by Lapcharoensap *et al.* (44) in 2018.

A Finnish study by conducted in 1996–1997 showed that a normally developed ELBW infant had costs 25-fold that of healthy term control infants, a mildly disabled ELBW had costs 33-fold, and a severely disabled ELBW infant had costs 68-fold those of control infants (45). In ELBWs, initial hospital costs alone accounted for 64% of total costs whilst the costs during the first and second post-discharge years accounted for 20% and 13%, respectively. Another study in Finland studying preterm births less than 32 weeks GA during the years 2000 to 2003 by Korvenranta *et al.* (46) showed that 89–93% of the total hospital costs, including the cost of morbidities in the first 4 years of life, was spent in the first year, and the initial hospitalisation costs comprised up to 84% of this total cost, and this pattern of distribution was similar for all GAs.

Societal costs of prematurity

A decision analytical model using Markov process to estimate the societal costs of preterm birth throughout childhood in the United Kingdom setting by Mangham *et al.* (47) demonstrated that the incremental cost per survivor till 18 years of age, borne by the public sector for preterm infants of 23 and 24 weeks GA were about $380,000 and $275,000 respectively compared to a term infant, a significant jump from an incremental cost of $130,000–$145,600 for those of 25 to 27 weeks GA compared to term.

The incremental in-hospital resource cost per survivor and quality adjusted survival, up to 2 years of age, for the extremely low gestation of 23 to 24 weeks was concluded as similar to that as at 25 to 27 weeks by the Victorian Infant Collaborative Study Group comparing the pre surfactant and post surfactant eras in the late 1990's (48). With improvements in neonatal intensive care over the past five decades, the limits of viability have reduced to around 24 weeks' gestation. While increasing survival has been the predominant driver leading to lowering the gestation at which care can be provided, these infants remain at significant risk of adverse long-term outcomes including neuro-developmental disability (49,50). In 1997, the quality-of-life (QOL) weightage in 23–24 weeks GA infants in Australia were estimated at 0.260–0.306 compared to QOL weightage of 0.598–0.717 in those 25 to 27 weeks GA (48). The post discharge health costs, rehabilitation and special education facilities for surviving infants born between 23–25 weeks GA using the EPICURE study findings (51) were an additional $4,200 per infant per annum compared to control term classmates. This costing can assist in resource allocation from the public sector if NIC is to be offered to infants at 23–25 weeks GA.

From Doyle *et al.*'s study (48), there were 80 more assisted ventilation days per additional survivor at 23 weeks gestation compared to one of 25 weeks GA. Therefore, even if additional funds were available in under-resourced countries, there will be a shortage of ventilator beds for the larger preterm infants. In addition, rehabilitation and special educational facilities are not well developed throughout LMICs.

Petrou *et al.* (8) projected that the bulk of additional costs post-discharge from hospital fell on the health and social care sectors under same decision analytical study above by Mangham *et al.*, ranging from 60% of total childhood costs for the very preterm (28–31 weeks GA), 48% for the moderate preterm group, 30% for the late preterm as compared to 15% for term infants. The incremental societal cost per very preterm child surviving to 18 years compared with a term survivor was estimated at $107,647. The corresponding incremental societal cost estimate for moderate preterm was $63,144 and for a late preterm child was $18,662. On concerns that preterm births would pose a major economic burden on special education, social welfare, rehabilitative, familial and other societal costs, Mangham *et al.* (47) estimated that one third of the public sector economic burden is borne during the neonatal period and that hospital inpatient costs are responsible for 92% of the incremental costs per preterm survivor at the various GAs compared to term infants (46,47). Therefore, offering high-quality neonatal intensive care to promote better short-term outcomes and reduction of days of hospitalisation and to prevent later morbidities in very preterm survivors should have a beneficial long-term effect on the cost per quality adjusted life year (QALY) (46).

Costs analysis of neonatal intensive care

The term "health economic evaluation" refers to health technology assessments that compare costs with the consequences of the interventions. Cost effective analysis (CEA) measures the costs of differing interventions to measure the same kind of consequences (such as survival rate or reduction in the incidence rate of NEC), expressed as incremental cost effectiveness ratio (ICER). Cost utility analysis is a specific type of CEA used to value outcomes according to preference based measures of health, e.g., quality-adjusted life years (QALY) or disability-adjusted life years (DALY) (1,15). The threshold that has been used by many countries to determine if a particular intervention is cost-effective is when the ICER per QALY gained or per DALY averted is less than 3 times the country's annual gross domestic product (GDP) per capita, and highly cost-effective if the ICER per QALY gained is less than the annual GDP per capita (52). With cost benefit analysis, the consequences are expressed in monetary terms.

The threshold that the public sector or health insurance programs have used for supporting a new technology or innovation has been $50,000 which was the cost per QALY gained for peritoneal dialysis. However, with the increased cost and newer technology, the ICER for hemodialysis as compared to no dialysis is $110,814 in 2009 US dollars (53). Cutler's paper (3) mentioned that from a study by himself and E. Richardson in 1990, weightage of QOL given for most severe conditions such as cancer, heart disease, paralysis were in the range of 0.65 to 0.75, and that most studies found a value of life at $75,000 to $100,000 per year for a middle-aged person.

The costs per QALY for neonatal care in 1990 dollars were $6,101, $1,290, $3,833 and $955 for those less than 1,000 gm birthweight, 1,000–1,500 gm, 1,501–2,500 gm and more than 2,500 gm birthweight respectively. This compares favourably with the cost per QALY for hemodialysis and compared to coronary artery bypass of $33,600–48,300 per

QALY in 1990 dollars. For infants between 1,000–1,500 gm birthweight, the lifetime costs were found to have increased from 1960 to 1990 but the developmental problems had reduced by 40% (3).

The cost benefit of ELBW survivors with an expected additional life expectancy of 30 years in 1990 and a QALY of 0.78 was $1.3 million per QALY, which is a high rate of return of 791% (3). The life-time medical costs of an ELBW infant is approximately $450,000 and assuming that the life expectancy of NICU survivors is 70 years with a QOL weightage of 0.7 compared to a term infant, the calculated cost of NIC care is $9,100 per ELBW infant per QALY (3,48,54,55). In a "worst-case" scenario of a life expectancy of 30 years and a QOL weightage of 0.4, the calculated cost would be $38,000, way below the cost of adult ICU costs of more than $100,000 per patient per QALY, and considered highly cost-effective.

In a more recent study in Finland, for children born at GA less than 32 weeks, the average cost per QALY at 4 years of life was $28,290, ranging from $17,381 to $79,856 (in 2008 dollars) and increasing with decreasing GA and more than twice the cost per QALY for children with two or more morbidities at the age of four. The corresponding cost per QALY for full-term controls was $1,736 in 2008 dollars (46). For Mexico, Profit *et al.* (56) showed NICU care for preterm infants to be very cost effective with ICER for NICU compared to no-NICU at approximately $1,200 per DALY for the 24–26-week GA group, $650 per DALY for 27–29 weeks GA, and $240 per DALY for 30–33 weeks GA.

From the Global Burden of Disease Study 2013, it can be seen that the DALY for preterm birth complications, neonatal jaundice, neonatal encephalopathy and congenital anomalies have been decreasing from 1990 to 2005. Further reduction in DALY were obtained for preterm birth and neonatal encephalopathy from 2005 till 2015 (57). It is anticipated ICER analysis of current outcomes will show lower incremental costs per GA compared to the studies mentioned above which were looking at the long-term outcome of infants born beyond a decade ago (58).

Strategies to reduce neonatal intensive care costs

The overall cost of NIC is increasing with new health technologies, increasing number of preterm births in the developed countries as a result of artificial reproductive technology and obstetric interventions (16), and increased number of moderate and late preterm births.

While neonatal intensive care is highly cost-effective, efforts could be made to reduce costs by practising comparative effectiveness monitoring whereby clinicians and institutions are encouraged to substitute inefficient or non-evidence based strategies for cost-effective clinical strategies in order to cut costs without adversely affecting health outcomes (59). Richardson *et al.* (60) described how there are variations in the days of ventilator use, use of antibiotics, laboratory tests ordered, use of vasopressors and sedation for apparently similar patients with no difference in health outcomes but with increased costs. This increased expenditure is due to higher intensity of care required and increased duration of stay in the NICU. All cost reduction strategies for NIC have to reduce either or both intensity of care and duration of NICU stay. Training programs to change clinician practices, enhance the use of protocols and empowerment of nurses to do neonatal resuscitation, as well as better technology has helped to markedly improve neonatal survival in China. In addition, whilst nosocomial infection rate remained the same, there was a reduction in antibiotic usage (31).

New technologies which are costly would only be feasible if they are offset by health benefits. In order to increase cost effectiveness, evidence based innovations and technologies aiming to improve survival and reduce morbidities have been reviewed. Reference can be made to Dukhovny *et al.* (1) who gives a stepwise approach to interpreting the validity of economic evaluations conducted alongside randomised controlled trials.

Eleven interventions (as in *Table 1*) already practised in well-resourced countries, including obstetric and perinatal care, have been found to have moderate to high-quality evidence to improve survival of preterm infants and recommended to be instituted in low to middle income countries (61).

Health care that is beneficial and reduce costs are rare—one of these is the use of antenatal steroids which has been clearly shown to reduce mortality, severity of RDS, risk of IVH, necrotising enterocolitis, severe disability rate and retinopathy of prematurity (62-65). There was a 14% reduction in cost per additional survivor (63). Delivery of this cost-effective intervention requires good antenatal follow-up, credentialing of midwives to give easy accessibility to delivery centres and that can still be challenging in low income and LMIC (66).

The other intervention that has been beneficial and reduce cost is surfactant replacement therapy as published in a review by Rushing *et al.* (63) where it was calculated

Table 2 Recommended strategies to improve cost-effectiveness of neonatal intensive care

Implementing strategies to improve survival of preterm babies such as in *Table 1*
Reduce the number of unwarranted deliveries between 34–37 weeks gestational age
Strategies such as comparative effectiveness monitoring to reduce unwarranted intensity of care and to reduce duration of hospital stay in NICU
Equitable government resources for perinatal health and high quality NICU services compared to adult intensive care services
Legislation to guide limited embryo transfer and financial support for limited ART cycles

NICU, neonatal intensive care unit; ART, assisted reproductive technology.

to have reduced costs per additional survivor by 9%. Early surfactant treatment has been shown to reduce days of ventilation and BPD (67). Similarly, current recommendations to reduce need for ventilator use and reduce risk of chronic lung disease is to use very early non-invasive respiratory support, such as in the delivery room and selective use of surfactant for those infants at risk of respiratory distress syndrome (68,69). In India, barrier to the usage of surfactant has been described as due to financial costs borne by the families, lack of availability of ventilators and lack of experience in instilling surfactant (70). However, the use of indigenous continuous positive airway pressure (CPAP) innovations have helped to provide CPAP to the larger preterm babies with successful treatment of RDS (71).

Exposure to any amount of formula milk in the first 14 days of life increased the risk of NEC by threefold in a prospective study by Johnson *et al.* (72). After controlling for NEC, it was calculated that each additional mL/kg/d of human milk reduced hospital costs by $562. A single standard deviation increases in the average dose of human milk during days 1–14 was associated with about $10,000 lower NICU hospitalization costs per infant. A prospective CEA study (73) using a randomised controlled trial in 323 VLBW infants of donor human milk (DHM) or preterm formula when mother's milk was not available, showed that there was a decreased incidence of NEC in the group supplemented with DHM. The ICER per NEC case everted with DHM was $5,328 (in 2015 Canadian dollars) at the time of discharge but there was no difference in costs between the two groups if post-discharge costs to 18 months of age were included due to lower wages received by mothers giving DHM. This shows the importance of including post-discharge costs in health economic evaluation. This study and the cost of DHM ranging from $4.00 to $5.00 per ounce, and the human milk fortifier costing $6.25 per mL (43) makes the cost effectiveness of using DHM unclear for prevention of NEC.

To address the rising cases of preterm infants due to assisted reproductive technology (ART) practices, more than 80% of the 70 countries surveyed had legislation, guidelines or both to guide ART practice (74) but only 10% of responding countries had limited embryo transfer in their legislation as of the year 2015. In Belgium, limiting the number of embryo transfers and paying only for 6 ART cycles by the public has led to a 50% reduction in multiple livebirth rate and 13% reduction in costs for maternal health and the children up to 2 years of age (75).

In conclusion, it can be seen that the majority of literature studying NICU costs reports on the cost of caring for the preterm infants. Although NIC is expensive, it is highly cost-effective according to standards of threshold and in comparison to many adult health care interventions. Significant cost savings can be obtained not by restricting the GA for which NIC is provided by the public sector or insurance policies, but rather, as given in *Table 2*, by reducing the number of preventable moderate and late preterm infants, improving neonatal outcomes through high quality NIC, implementing comparative effectiveness monitoring of clinical strategies as well as strengthening public health measures in antenatal, perinatal care and essential newborn care for the low and middle income countries.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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