HEALTH TECHNOLOGY ASSESSMENT OF AUTOMATED RESUSCITATION DEVICE FOR NEONATAL RESUSCITATION AT POINT OF DELIVERY IN INDIAN HEALTHCARE SYSTEM

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Study Title: Health Technology Assessment of Automated Resuscitation Device for Neonatal Resuscitation at point of delivery in Indian Healthcare System

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List of Abbreviations

ARD	Automated Resuscitation Device
BPD	Bronchopulmonary dysplasia
DALY	Disability Adjusted Life Years
ICER	Incremental Cost Effectiveness Ratio
IVH	Intraventricular Haemorrhage
NICU	Neonatal Intensive Care Unit
OWSA	One Way Sensitivity Analysis
PSA	Probabilistic Sensitivity Analysis
PVH	Periventricular Malacia
SIB	Self-Inflating Bag
TDABC	Time Driven Activity Based Costing
UNICEF	The United Nations Children's Fund
WHO	World Health Organization
YLD	Years Lost due to Disability
YLL	Years of Life lost
NMR	Neonatal mortality rate
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
IMR	Infant mortality rate
NFHS	National Family Health Survey
LBW	Low Birth Weight
CPR	Cardio-Pulmonary Resuscitation
PEEP	Positive end-expiratory pressure
CPAP	Continuous positive airway pressure
PIP	Peak inspiratory pressure
IPPV	Intermittent positive pressure ventilation
FIO2	Fraction of inspired oxygen in the air

Contents

Executive Summary

India has the highest number of neonatal mortality rate. It accounts for one fifth of under-five mortality burden and a quarter of neonatal deaths globally. The commonest causes of neonatal mortality in our country are pre-maturity/preterm (35 per cent); neonatal infections (33 per cent); intra-partum related complications/ birth asphyxia (20 per cent); and congenital malformations (9 per cent). The states of Uttar Pradesh, Madhya Pradesh, Rajasthan and Bihar account for more than half of new-born and under-five deaths in India.

The Systematic Review on Incidence and Prevalence of Neonates with Birth Asphyxia within 28 days from day of birth in India concludes that the neonatal morbidity and mortality due to birth asphyxia can be prevented with the use of an effective resuscitator device.

We have done a Health Technology Assessment for a new automated resuscitator device (ARD) in comparison to Self-Inflating Ambu Bag (SIB) which is the current Standard of Care. The new resuscitation device claims to provide effective resuscitation with the automatic equipment which requires minimal skill and training. Additionally, due to other associated modes of CPAP and bubble CPAP, ARD could also support in stabilizing new-born post recovering from resuscitation until the neonate is transferred to District hospital as per medical advice. We did a survey among practitioners such as NICU doctors and nurses to find out the operational challenges they face while using ARD or SIB, and whether ARD can address those challenges. Even though there is limited evidence on clinical effectiveness of ARD, the evidence does suggest a reduction in severe cases, mortality and intubation rates when compared to the standard of care, SIB.

To assess the cost-effectiveness of the device at the Tertiary level healthcare setting in Andhra Pradesh, we constructed a decision analytic model to compare the device to standard of care- Self Inflating bag.

We checked the robustness of our results by deterministic one-way sensitivity analysis and probabilistic sensitivity analysis. The Incremental Cost Effectiveness ratio (ICER) for the new device when compared to self-inflating bag is – 4755.95 Rs/DALY averted. The negative ICER value implies that the new device is both clinically and cost effective compared to the standard of care. In order to check the robustness of these results, we ran Monte-Carlo simulations and found that new device would be cost-effective with 95% probability at Rs 5000/-. Based on the Incremental Cost Effectiveness ratio value we obtained, the ARD device reduces both the cost and averts Disability adjusted life years by the virtue of reducing the number of severe cases caused due to birth asphyxia. Based on this analysis, the device can be used at a tertiary level healthcare setting in Andhra Pradesh.

Lastly, we did a budget impact modelling for the five states in India with the worst Neonatal mortality rates to find out what impact would it have on the exchequer of these states with gradual switchover to ARD device from current Standard of Care (SIB). We found that the gradual switch to ARD from SIB

would lead to net cost savings for all the top five adversely affected states in India by neonatal birth asphyxia.

We recommend a pilot study in any part of India in order to collect more accurate data on operational challenges and to find the cost of training.

AIM AND OBJECTIVES

Aim:

Health Technology Assessment of automated resuscitation device for neonatal resuscitation at point of delivery in Indian healthcare system.

Objectives:

- To assess the cost effectiveness of automated resuscitation device compared to self-inflating bag at point of delivery in public healthcare system at tertiary level in India
- To synthesize the evidence on clinical effectiveness of the automated resuscitator device.
- To assess the feasibility and scaling up of automated resuscitation device.

Population	Birth asphyxiated new-borns requiring resuscitation in Public health care settings.
Intervention	Automated Resuscitation Device (type of T-piece resuscitator)
Comparators	Self-inflating bag
Outcome	Primary Outcome: - Incremental cost effectiveness ratio (ICER) - Disability Adjusted Life Years (DALYs) Secondary Outcome: - Intubation rate - Mortality rate
Time horizon	Lifetime
Perspective	Societal

Chapter 1.A Systematic Review on Incidence and prevalence of neonates with birth Asphyxia within28 days in India

1. Introduction

The neonatal period is a very vulnerable period of life due to many problems, in which most of the cases is preventable. It is estimated that 130 million neonates are born each year and out of these, 4 million die in the first 28 days of their life (neonatal period), 50% of all deaths are within first 24 h while 75% are within first 7 days of life [1]. Perinatal mortality refers to the number of stillbirths and deaths in the first week of life and India alone contributes to 25% of neonatal mortality around the world [2]. Neonatal period is defined as time period up to first 28 days of life and further divided into very early (birth to <24 h), early (birth to <7 days), and late neonatal period (7 days to <28 days) [3]. India has the highest Neonatal Mortality Rate (NMR) which is defined as a death during the first 28 days of life. As many as 1.09 million children die annually. While the NMR rate varies by state, the overall country rate was reported to be 43 per 1000 live births [4]. Infant mortality rates (IMR) vary from state to state across the country, as the efforts and consistency towards child survival varies.

Infant mortality rate (IMR) in a population specific to a year is defined as the number of deaths in children <1 year of age per 1000 live births occurring in the same year. The rate is historically regarded as a good proxy measure of population health and has been shown to bear strong association with other comprehensive measures of people's health such as disability adjusted life expectancy [5]. Although India has witnessed a fast decline [6] in IMR in the recent past - an impressive average drop of 4.56% per year over the last 5 years, concerns have been raised on substantial differences in achievement in this regard between regions within the country and even between districts within a State [7]. Appendix-4 shows the state wise distribution of Neo-natal mortality rate.

1.1 Epidemiology

Asphyxia is a condition where oxygen deprivation occurs around at the time of birth. There is an impairment of blood-gas exchange, resulting in hypoxemia (lack of oxygen) and hypercapnia (accumulation of carbon dioxide), which results in biochemical changes inside the body leading to brain damage and neuronal cell death. Continuous asphyxia will also lead to multiple organ systems dysfunction. Birth asphyxia is a serious clinical problem worldwide and contributes greatly to neonatal mortality and morbidity [8]. During the neonatal period the first 28 days of life carries the highest risk of mortality per day than any other period during the childhood. Approximately 10% of newborn babies fail to initiate effectual breathing at birth. Most of these start breathing after initial stimulation by the health personnel, about 3-5% need basic resuscitation, <1% require advanced resuscitative effort to achieve efficient circulation to the vital organs [9]. From four million annual deaths about ninety-nine percent of neonatal deaths occur in low middle-income countries, where most births occur at home without a skilled attendant. Another one million children who survive birth asphyxia live with chronic neuro-developmental morbidity, including cerebral palsy, mental retardation, and learning disabilities, although there is significant uncertainty regarding this estimate [10]

1.2 Indian scenario

In India alone, around one million babies die each year before they complete their first month of life, contributing to one-fourth of the global burden [11]. The neonatal mortality rate (NMR) in India was 32 per 1000 live births in the year 2010, a high rate that has not declined much in the last decade [12]. In recent years the NMR has dropped by 15%, that is from 40 per 1000 live births in 2001 to 34 per 1000 live births in 2009. The common causes of neonatal deaths in India include infections, birth asphyxia, and prematurity which contribute to 32.8%, 22.3%, and 16.8% of the total neonatal deaths, respectively [13].

1.3 Risk of birth asphyxia

Risk factors of birth asphyxia has been divided into antepartum, intrapartum and foetal. Risk factors include increasing or decreasing maternal age, prolonged rupture of membranes, meconium stained fluid, multiple births, non-attendance for antenatal care, low birth weight infants, malpresentation, augmentation of labour with oxytocin, ante partum haemorrhage, severe eclampsia and pre-eclampsia, ante partum and intrapartum anaemia [14]. The prognosis and severity of the symptoms of child with birth asphyxia depend on the risk factors and management of the patient. Although the majority of births take place in hospitals, the deliveries that took place at home and private clinics were more prone to the risk of developing Birth asphyxia.

2.AIM

To map the incidence and prevalence of Birth Asphyxia in neonates below 28 days in India.

2.1 Objective

- To conduct a meta-analysis to find out the average Incidence, Prevalence rates of Birth Asphyxia in Neonates below 28 days based on secondary literature data.
- To find the Morbidity and Mortality rates of birth asphyxia based on secondary literature data.
  - **Content**: Neonatal burden with Birth Asphyxia in India
  - **Condition**: Incidence, prevalence, Mortality and Morbidity of Birth asphyxia of neonates below 28 days
  - **Population**: Neonates with birth asphyxia below 28 days.

2.1Methodology

2.2.1 Literature search databases

The systematic review was conducted by primary electronic database search. Searches were conducted in PubMed, Google scholar and Cochrane data bases. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was developed for this project. The time taken to complete this study was approximately 5 months. The articles included in this study were from the period 2012-17.

2.2.2 Inclusion criteria

Articles were considered for inclusion if the study met the following criteria: --liveborn neonates, 28 days of neonates, rural and urban conditions of child birth, low birth weight, asphyxia and prematurity**.**

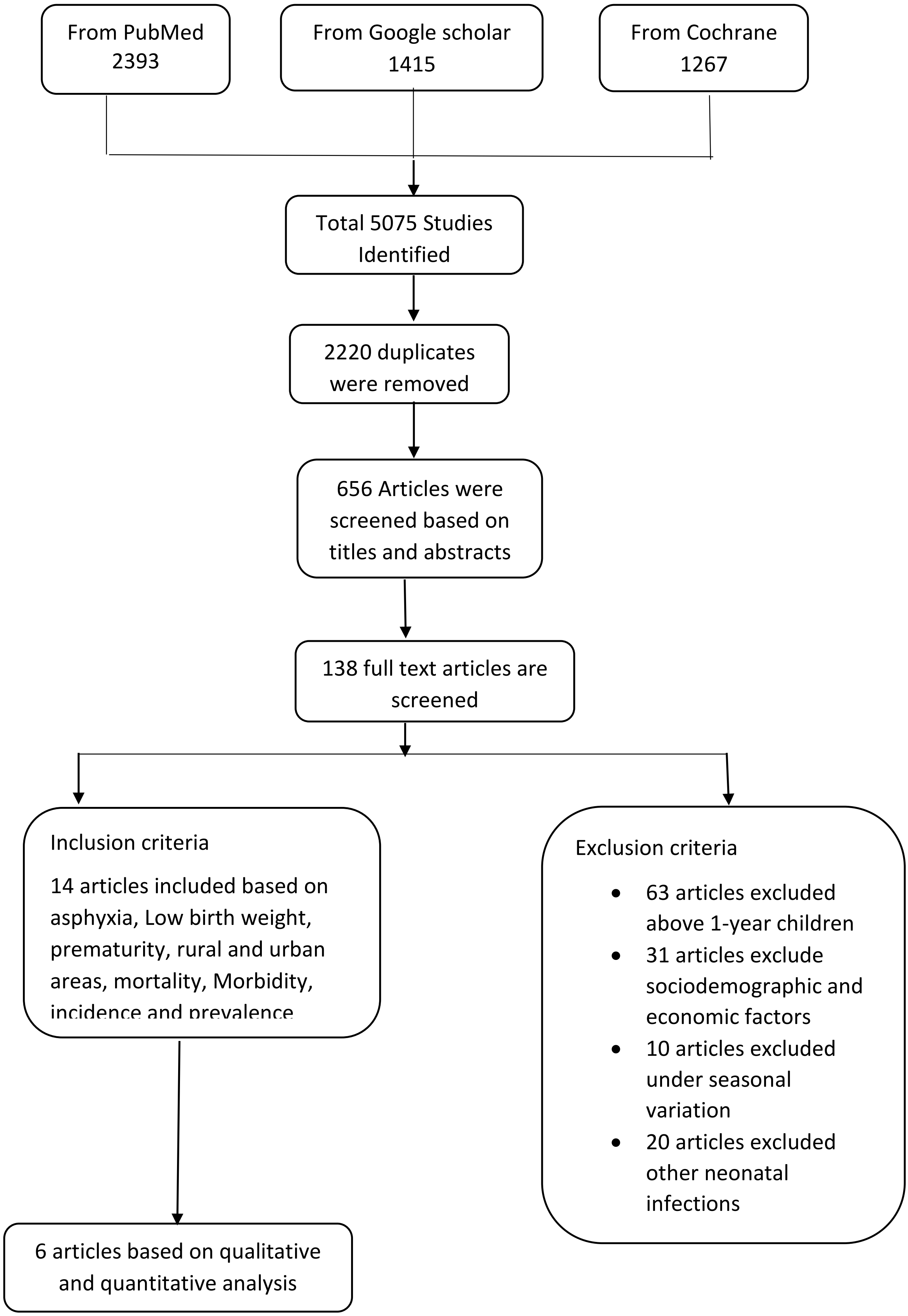
2.2.3 Exclusion criteria

Excluded studies in which researchers did not provide data, neonates above one year, socio demographic and economic factors, seasonal variations in asphyxia and other neonatal infections

2.2.4 Screening process

All articles identified by the search were initially screened for eligibility on title and abstracts. The search results were exported to the reference management software EndNote X7. Duplicate articles were removed and the remaining titles and abstracts were screened. Full-text articles were retrieved and assessed for eligibility using predefined criteria, for inclusion in the review. The target population was neonates defined as babies aged 0–28 days.

2.2.5 Prisma flow chart



2.3 Keywords

Neonates, mortality, morbidity, asphyxia, Incidence and prevalence

2.4Types of studies

The studies like prospective, Retrospective, Observational and cross-sectional studies.

2.5 Data extraction

All articles were reviewed independently, extracted into a standard Excel file, then all studies that fulfilled the inclusion criteria were included and those studies that are lacking required data were excluded.

2.5.1 Study quality assessment

Individual studies were evaluated for qualitative study where the context, condition and population were taken into consideration. Neonatal morality is the largest burden contributing to nearly two-thirds of the total infant mortality in most developing countries. Neonatal mortality is the probability of dying in the first month after birth and post-neonatal mortality is the probability of dying after the first month of birth but before completion of one year [15]. Many morbidities such as preterm birth, low birth weight (LBW), or asphyxia ‘‘occur’’ at the time of birth. The remaining morbidities appear at different times during days 1 to 28. In Indian context, majority of deliveries and neonatal deaths occur at home and are usually not attended by health professionals. Secondly, many factors that contribute to neonatal mortality have their origin long before a baby is born. These are termed ‘endogenous’ causes, and are primarily influenced by genetic make-up or circumstances arising before or during birth. The neonatal period, the first 28 days of life carries the highest risk of mortality per day than any other period during the childhood. Asphyxia is an important cause of neonatal morbidity and mortality. Mild asphyxia was defined as no cry, or breathing absent or slow, weak or gasping, at 1 minute after birth. Severe asphyxia was defined as breathing absent or slow, weak or gasping at 5 minutes after birth. The incidence of mild asphyxia was relatively high, but it did not show association with risk of death. Severe asphyxia showed high risk of death [16].

While the ‘‘incidence’’ represents the occurrence of new cases, the total number of cases, old and new, at any given point of time is represented by the ‘‘point prevalence’’. Their prevalence markedly decreases during 2 to 4 weeks. Asphyxia is one of the neonatal morbidities requiring inpatient hospital observation, admission or readmission during the first 7 days of life. The incidence of morbidities increased from 23% at 40 weeks to 30%, 39.7%, 67.5%, 89% and 87.9% at 38, 37, 36, 35 and 34 weeks, respectively. The prevalence of birth asphyxia registered for children born to educated mothers is several times lower compared with those born to uneducated/illiterate mothers.

Neonatal mortality was around 45 per 1000 live births in 2000 in India compared with just about 4 per 1000 live births in most developed countries [15]. In most populations, male mortality is generally higher than female mortality for all ages, because males are considered biologically weaker than females and thus have greater vulnerability to infectious diseases and higher risk of mortality [17]. Neonatal mortality in this analysis is defined as infant deaths that occur in the first four weeks of life (0–28 days) [18].

2.5.2 Critical appraisal

Risk of Bias: Risk of bias summary: review authors' judgements about each risk of bias item for each study included.

a) Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

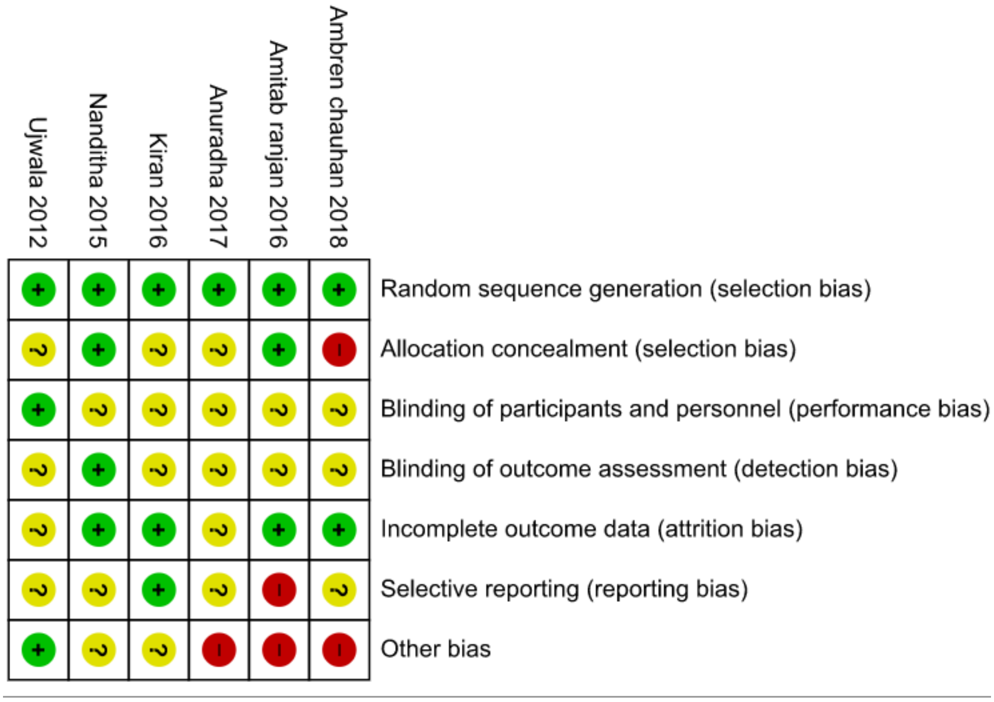


Fig. 1. Risk of bias summary

b) Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies. Both risk of bias Graph and risk of bias summary states that the selected studies have low risk of bias, unclear risk and less studies showed high risk

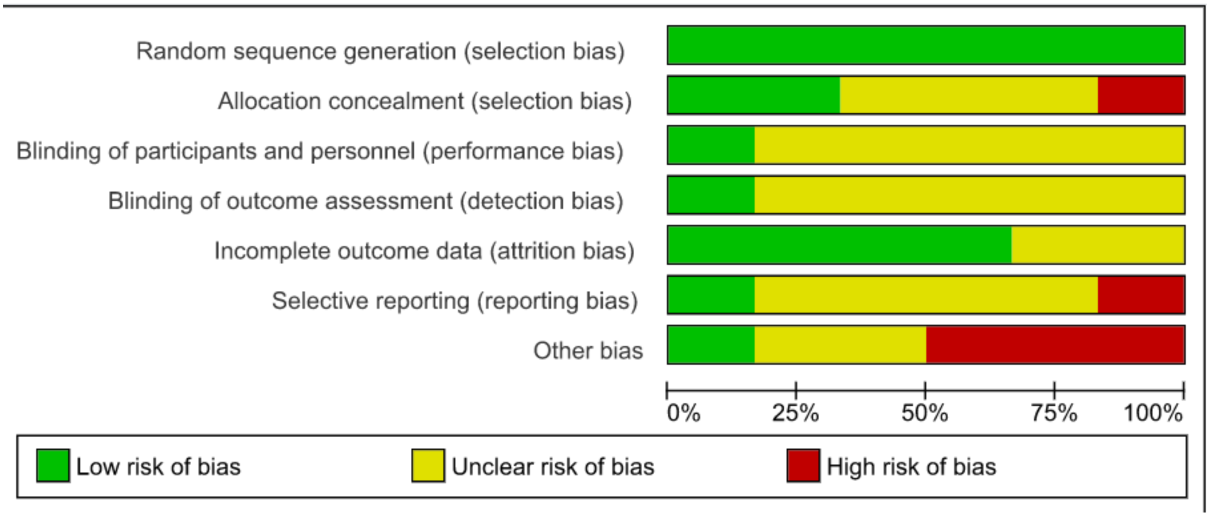


Fig. 2. Risk of bias graph

The analysis of risk was completed using Cochrane RevMan 5.0. This exercise is pivotal to knowing the quality of the data used.

3. Results

3.1 Study selection

A total of 5075 articles were identified by the search strategy of different databases like PubMed, Google scholar and Cochrane of which 2220 were removed based on duplicates, 656 articles were removed based the title and abstract. The full texts of 139 articles were screened, of which 14 articles met the inclusion criteria and were included in this review and 6 articles were taken into consideration based on the qualitative and quantitative analysis.

3.2 Study characteristics

The neonates with below 28 days suffering with asphyxia will be treated immediately. In the present study, detection and reporting bias were taken as criteria. Detection bias considered only neonates below 28 days suffering with asphyxia for treatment while the reporting bias considered the outcomes of patients if they recovered from this condition of asphyxia,

3.3 Description of the included studies

Table: 1 List of Included studies

S.no	Author	Year	Total	Birth asphyxia below 28 days	Study period	Study design
1	Ujwala[20]	2012	105	21	2005-07	Prospective study
2	Amitab Ranjan[24]	2016	4457	1162	Jan2012-Dec 2015	Retrospective, analytic and descriptive study
3	Nanditha[23]	2015	427	124	Jan 2010-june 2012	Observational cohort study
4	Kiran Panthee[25]	2016	425	82	Dec 2014-Nov 2015	Retrospective study
5	Ambren Chauhan[27]	2018	1000	220	Jun 2016-May 2017	Cross-sectional study
6	Anuradha[28]	2017	2927	400	Jan 2013-April 2017	Retrospective observational study

3.4 Study outcome

3.4.1 Primary outcome:

3.4.1.1 Incidence

The primary outcome is asphyxia in neonates below 28 days and secondary outcome is mortality rate of neonates below 28 days. In an retrospective and analytical with a study period of one year, and a study group of a total of 4714 neonates who fulfilled the inclusion criteria, 171 babies suffered from birth asphyxia (3.63%). The incidence of birth asphyxia in this was found to be 36 per 1000 live births. Out of the 171 asphyxiated neonates, mortality was seen in

50, hence asphyxia related mortality was 10.6 per 1000 live births. Mortality in only full-term babies was reported as 3.3 per 1000 live births [19].

Table: 2 Incidence of birth asphyxia in neonates below 28 days in India

S.no	Author	Year	Total	Birth asphyxia below 28 days	Incidence%
1	Ujwala[20]	2012	105	21	14%
2	Amitab Ranjan[24]	2016	4457	1162	20.99%
3	Nanditha[23]	2015	427	124	29%
4	Kiran Panthee[25]	2016	425	82	19.30%

In a prospective study for the period October 2005 to September 2007, for an incidence of 105 births, 21 babies suffered with birth asphyxia showing the incidence rate of 14% [20]. In a retrospective study in the period of Jan 2014- Dec 2014, for 1000 live births, the birth asphyxia was reported with an incidence rate of 17.72 [2]. In a recently provided data on the timing of cause-specific neonatal deaths, almost all deaths (97.8%) due to asphyxia occur in the first week of life, with 70% of them occurring within the first 24 h (day 0) [21]. In another study, based on gender, there were more male babies (52) asphyxiated when compared to female babies (32). Out of a total 3507 deliveries, there were about 3130 near-term and term babies, among whom 84 babies had birth asphyxia (they are enrolled for the study). The incidence of birth asphyxia among near-term and term babies in the study was 2.7% [22]. In an observational cohort study design in the study period of Jan 2010- June 2012, with a study population of 427 neonatal, birth asphyxia was 124 with an incidence of 29% [23]. A retrospective, analytic and descriptive study design in the study period of Jan 2012-Dec 2015 comprised of total 4457 neonates, out of which 1162 are with birth asphyxia with an incidence of 20.99% [24]. In a Retrospective study design in the study period of Dec2014- Nov 2015, birth asphyxia was 82 among a population of 425 neonates with an incidence of 19.3% [25].

3.4. Prevalence

Table: 3 Prevalence of birth asphyxia in neonates below 28 days in India

S.no	Author	Year	Total	Birth asphyxia below 28 days	Prevalence%
2	Ambren Chauhan[27]	2018	1000	220	38.20%
3	Anuradha[28]	2017	2927	400	13.60%

In a cross sectional study design with a study period of Jun 2016-May 2017 comprising of a total 1000 neonates, prevalence of birth asphyxia was 20.99%[26]. Birth asphyxia prevalence was 19.3% in a Retrospective observational study design with a study period of Jan 2013-April 2017 for a population of 2927 neonates [27]. An observational cohort study design with a study period of one-year (2010) had 28.93 per 1000 live births prevalence of perinatal mortality. Prevalence of 56.9% (120) was noted among 211 neonates of both gender in a neonatal unit in a cross-sectional study conducted in January 2015 to December 2016 [28]. An observational cohort study design with a study period of Jan 2010- June 2012 observed a prevalence of 31.6%. Important rural–urban and socioeconomic differences in the NMR were also noted in the study, with the NMR in rural areas twice of that in urban areas (31 vs 15 per 1000 live births). The difference of NMR between the rural-urban was 60% or more in Andhra Pradesh, Assam, Jharkhand and Kerala. The mortality rate of neonates were 71.42% in rural and 25.58% in urban regions. Birth asphyxia in rural regions of the Maharashtra and Uttar Pradesh attributed to 25% and 23% of neonatal mortality respectively [29]

3.4.2 Secondary outcome

It is estimated that of 130 million infants born each year worldwide [30], 4 million die in the first 28 days of life. Three quarters of neonatal deaths occur in the first week of life, with more than one-quarter of these deaths occurring within 24 hours of the birth [1]. India alone contributes to 25% of neonatal mortality around the world. As per the National Family Health Survey-3 report, current neonatal mortality rate (NMR) in India is 39 per 1000 live births and birth asphyxia account for nearly (23%) of neonatal deaths [2]. A number of 22 neonatal deaths out of 1000 live births [31]. A recent prospective study [32] by provided data on the timing of cause-specific neonatal deaths reported that almost all deaths (97.8%) due to asphyxia occur in the first week of life, with 70% of them occurring within the first 24 h (day 0). Infant mortality rate (IMR) is regarded as an important and sensitive indicator of the health status of a community. It also reflects the living standard of the people and the effectiveness of interventions for improving maternal and child health.

Table: 4 Mortality rate of neonates with birth asphyxia

S.no	Study	Year	Total	Number
3	Shah[31]	2011	1000	22
4	P.V Sridhar[2]	2015	1000	57
5	Baqui[32]	2016	1000	97

The difference exists between Urban and rural with the mortality rates higher by 50% in rural (42.5/1000 live births) compared to urban (28.5/1000 live births) areas, as per the National Family Health Survey (NFHS-3) [33]. Morbidity of neonates for birth asphyxia is moderate and Early recognition of birth asphyxia and timely referral to tertiary centre can reduce morbidity and mortality

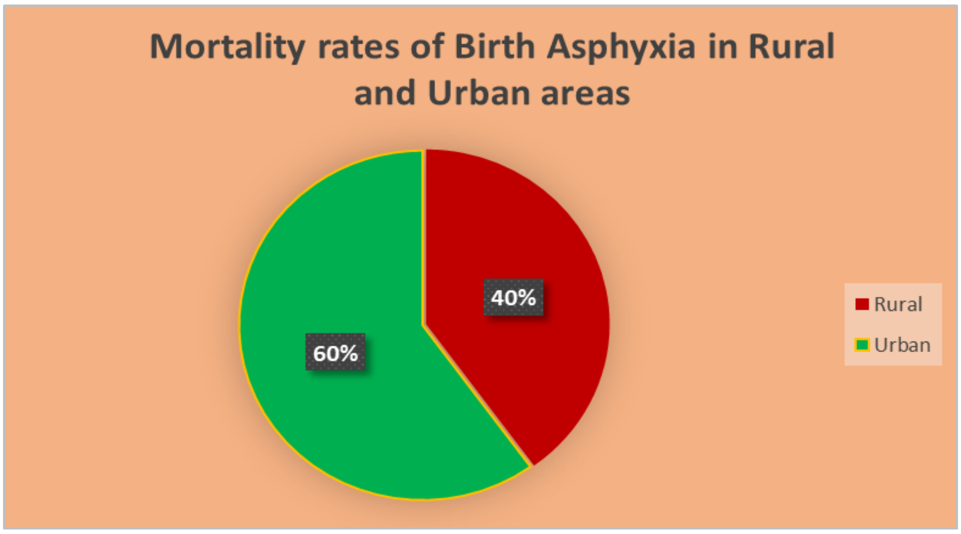


Fig. 3. Mortality rate of birth asphyxia in rural and urban areas

4.Sensitivity analysis

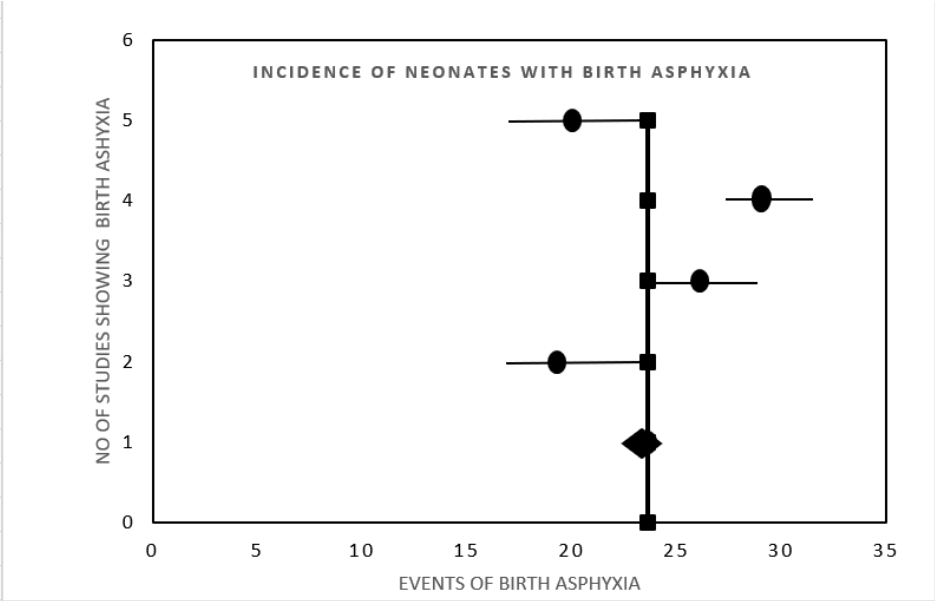


Fig. 4. Forest plot for Incidence of neonates with birth asphyxia

The forest plot (Fig.4) displays the number of events(incidence) of birth asphyxia on X axis and number of studies on Y axis. We compare the sample sizes and differences in variance and central tendency across each of the constructs. The grand mean is described by diamond on the vertical axis with its associated 95 percent confidence interval of upper and lower limits with the central tendency of 23.6

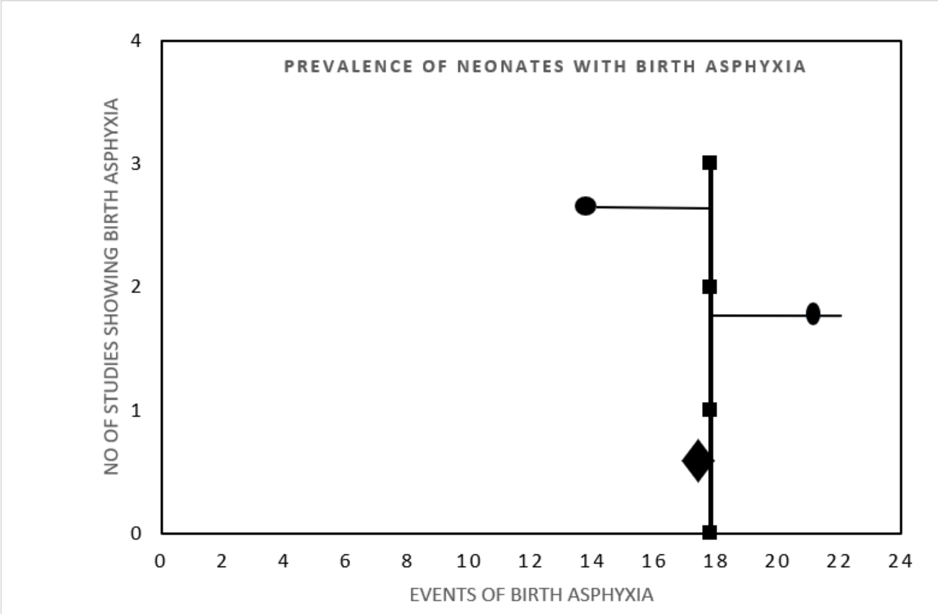


Fig. 5. Forest plot for Prevalence of neonates with birth asphyxia

The forest plot (Fig.5) shows the number of events(prevalence) of birth asphyxia on X axis and number of studies on Y axis. We compare the sample sizes and differences in variance and central tendency across each of the constructs. The grand mean is described by the diamond on the vertical axis with its associated 95 percent confidence interval, of upper and lower limits with the central tendency of 17.8

5 Discussion

The data show that the major cause of deaths during the neonatal period was birth asphyxia. In India approximately 9,40,000 neonatal deaths occurred during 2007, amongst which birth asphyxia contributed to about 19.5% in the mortality [34]. The prevalence of birth asphyxia in any community is to a large extent dependent on prevailing risk factors [12]. Prevalence of Perinatal Mortality Rate in the present study was 28.93 per 1000 live births which is well below the national average for rural community. Birth asphyxia has been reported as leading cause of perinatal mortality. It accounted for 10.6%, 26% and 26.2% of perinatal mortalities in studies conducted in Maharashtra [14], West Bengal [19] and Orissa [20] respectively. It accounted for 22% of the perinatal mortalities, which is similar to other studies.

6 Conclusion

Birth asphyxia is the medical condition resulting from deprivation of oxygen to a newborn infant that lasts long enough during the birth process to cause physical harm, usually to the brain. Birth asphyxia is one of the most common causes of admission to NICU and is also a leading cause of morbidities and mortality in newborn babies. Neonatal morbidities and mortality rates in India mostly depend on the socioeconomic factors, rural and urban divide, and other causes like Low birth weight, meconium-stained amniotic fluid, caesarean section, and prolonged maternal labor. The mortality and morbidity rates also varied from state to state**.** Further prospective and case control studies will be required, to get more scientific ideas about birth asphyxia and to develop strategies for its prevention and management.

Chapter 2: Evidence synthesis for clinical effectiveness of the device

1.1 Description of the Technology

As per Roehr et al 2018 [64]-" Worldwide, SIBs are the most commonly considered manual resuscitation devices, used in over 90% of NICUs. SIBs are intermittent flow devices operated by manual compression of a breathing bellow. Depending on the vigor of the operator's squeeze, they will provide varying pressures and consequently varying Vts, in particular as there is a large variety of SIBs available, with varying volumes, ranging between 220mL and 500mL for neonatal patients."

They also mention the disadvantages of SIB such as the unsuitability in reliably and consistently providing ventilation pressures (PIP and PEEP) and unsuitability in giving sustained inflation.

Regarding T-Piece the authors mention that "T-piece devices have become the accepted standard in most high-resource area DRs, either as portable, stand-alone devices or integrated in modern resuscitation platforms". The advantages mentioned for T-Piece resuscitator were – steady delivery of a set PIP as well as steady delivery of PEEP provision (and hence the ability to deliver both IPPV and CPAP) and the relative ease of use in terms of the inexperienced.

A qualitative review of the evidence of T-Piece resuscitator by Hawkes et al.(2012) [65] synthesized evidence on advantages and disadvantages of the T-Piece resuscitator. They are summarized in the following table:

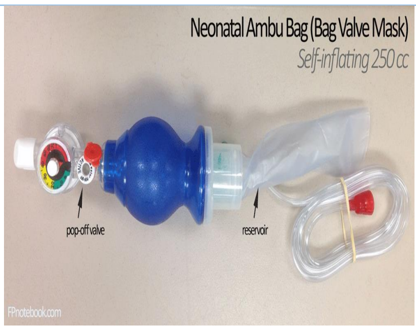
Table 5: Advantages and Disadvantages T-Piece resuscitator

Advantages	Disadvantages
Delivery of inflating pressures closer to predetermined target pressures with least variation	Technically more difficult setup
The ability to provide prolonged inflation breaths	More time required to adjust pressures during resuscitation
Consistent tidal volumes	A larger mask leak
	Less ability to detect changes in compliance

Following table describes the major differences between the two devices:

Table 6: Devices used for ventilation at the time of neonate resuscitation

	Self-inflating bag	T-piece resuscitation device (with manometer)
Needs pressurized gas source	No	Yes
Assists user to detect mask leak	No	Yes
Peak inflation Pressures	Inconsistent, may be high	Consistent, adjustable
Delivers PEEP or CPAP	No	Yes
Can deliver sustained inflation	No	Yes

		
Features	There are four parts of the self-inflating bag: - Air inlet, Oxygen inlet, Patient outlet, Valve assembly. Optional parts- Pressure gauge, PEEP valve, Bag with oxygen and Oxygen reservoir. <u>Use</u> [23] 1.To provide intermittent positive pressure ventilation 2.To provide peak end expiratory pressure in preterm babies 3. To judge pressure required before connecting baby to ventilator.	Infant T-piece resuscitator has the ability to set and control PIP as well as PEEP. The infant T-piece attaches directly to the patient interface and ventilation is accomplished by placing a finger over a hole on the exhalation side. Most infant T-piece resuscitators have an in-line manometer for continuous monitoring of the pressure.

1.1.1 Bag valve mask/ self-inflating bag

- A self-inflating bag refills itself when you stop squeezing it. Squeezing the bag inflates the lungs. Releasing the pressure allows the bag to refill with air as well as with oxygen if an oxygen source is attached.

1.1.2 Neonate Resuscitation Device:

The device features an integrated design, focused on safety operational reliability, consistency, accuracy and easy maintenance.

Components are manufactured using silicon and medical grade polymers.

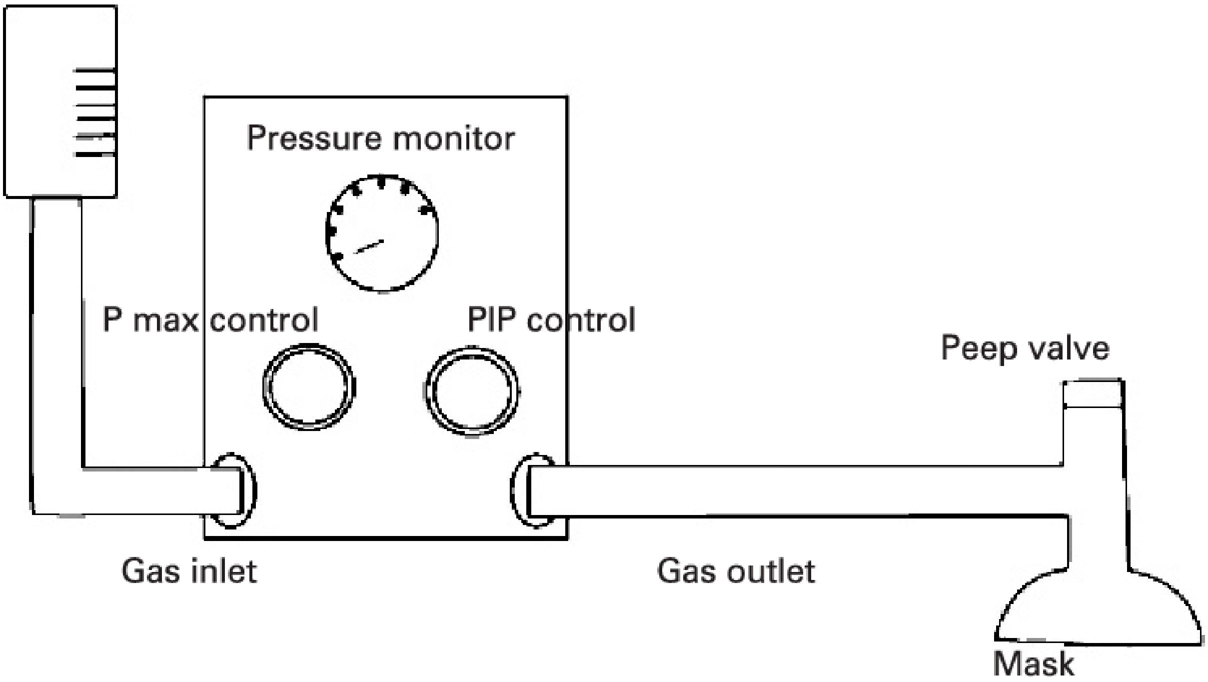


Figure:6 Diagram of the Automated Resuscitator Device (Hawkes et al. 2009[62])

Parts of device:

- Front Panel: User controls, patient settings and forms the main interface among the device, user and the patient. Front panel also houses an electrical on/off switch, fuse, tube connectors to connect the patient breathing circuit and the pressure dials to read the pressure.

- Real Panel: Rear Panel houses electrical supply connections (AC /Generator External battery). Rotameters to measure and control the Oxygen flow. Inlet to pneumatic controls.

- SS box: The front and the rear and the rear panel are mounted on the chassis of the SS cabinet and the devise is housed inside this SS cabinet.

Measurable Parameters of the devices:

- Respiratory Rate: Pre-set as per neonatal requirements
- Pressure: Displayed by an analog dial on the front panel
- Flow: As per neonatal requirements
- Tidal volume: As per neonatal requirements

Electric Power Supply:

The Electric Power Supply is responsible for powering the equipment and it consists of an AC power source. The Neonatal Respirator is compatible with an external power source such as a generator or UPS can be connected for use as and when required.

Pneumatic Component:

The Pneumatic Component is responsible for a) Air and oxygen flow b) Exhalation valve

a) Safety valve d) Oxygen flow control e) Intake filters.

Resuscitation Delivery System:

The resuscitation device is to target neonate population. It is intended for treating neonatal patients with respiratory failure or respiratory insufficiency and the resuscitation is achieved using the following procedure:

- User Interface—for selection of ventilation modes such as IPPV, CPAP, Bubble CPAP and setting the pressure
- Patient Breathing System—Connected to the front panel for delivering resuscitation parameters and facilitating exchange of gases

Process Flow:

The Respirator controls the air and oxygen flows by means of separate valves.

a. Oxygen flow to the unit is monitored and controlled by rotameters. Oxygen is only used in case if the FiO2 used is too high. Humidification is done by bubbling the gas through the water

b. Air and oxygen is mixed in the proportions required by the user by adjusting the valve of the rotameter which is then compressed to specific pressure and delivered to the Patient delivery Valve at specific pre-set time intervals

c. At the patient delivery valve the pressure can be set by the user

d. Exhaled air is sent out through the exhalation valve located in the Patient delivery valve

Power supply sources:

The Neonatal Resuscitator is capable of working by means of two different types of 1. AC Mains Power Supply Voltage: 240V, Frequency: 50 / 60 Hz. Consumption: single unit for 10 hours use, per baby used.

2. External UPS or Generator: As specified by the User.

As described neonate resuscitator is an automated resuscitator. The device support resuscitation by providing intermittent positive pressure ventilation (IPPV). The respiratory rate is pre-set in the device and as per clinical assessment of the neonate pressure and volume can be adjusted through control panel and checked through analog display. The device work on the principle of T-piece resuscitator. As described above T-piece resuscitator provide both IPPV and CPAP modes. The device also has additional advantage of bubble CPAP which could be used as per clinical advice. The device is compatible to support asphyxiated new-born as well help in maintaining their breath once spontaneous breath starts.

1.2 Systematic Review on the Clinical Effectiveness of the device

We did a Systematic review to find evidence on the clinical effectiveness and safety of the device.

1.2.1 Literature search databases

The systematic review was conducted by primary electronic database used was PubMed with supplementary searches conducted in Google scholar and Cochrane data base. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

1.2.2 Inclusion criteria

Articles were considered for inclusion if the study met the following criteria: Randomized controlled trials or prospective observational study on the clinical effectiveness of the T-Piece resuscitator

1.2.3 Exclusion criteria

Bench studies on the device, simulations and treatment recommendations were excluded.

1.2.4 Screening process

All articles identified by the search were initially screened for eligibility on title and abstracts the search results were exported to the reference management software EndNote X7. Duplicate articles were removed and the remaining titles and abstracts were screened. Full-text articles were retrieved and assessed for eligibility using predefined criteria, for inclusion in the review. The target population was neonates with birth asphyxia, which requires resuscitation.

1.2.4.1 Keywords

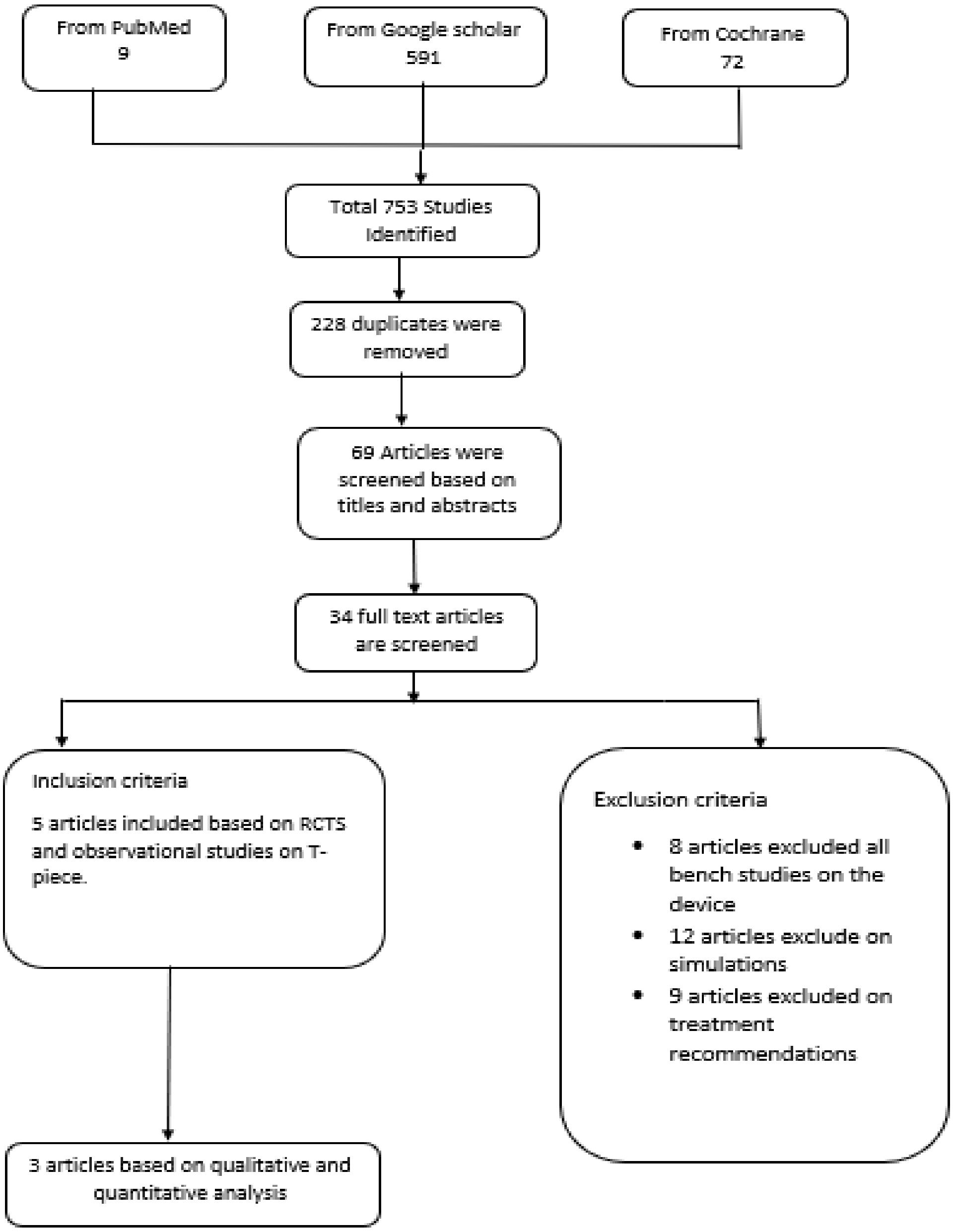
Neonates, Birth asphyxia, Mortality, T- Piece Resuscitation (ARD), Self-Inflating bag

1.2.4.2 Types of studies

Randomized control trails and prospective observational study

1.2.4.3 Data extraction

All articles were reviewed independently extracted into a standard Excel file, that all studies that fulfilled the inclusion criteria and those studies that are lacking required data were not be calculated.



PRISMA Chart

1.2.2 Results

1.2.2.1 Study selection

A total of 753 articles were identified by the search strategy of different databases like PubMed, Google scholar and Cochrane of which 228 were removed based on duplicates, 69 articles were removed based the title and abstract. The full texts of 34 articles were screened, of which 5 articles met the inclusion criteria and were included in this review and 3 articles were taken into consideration based on the qualitative and quantitative analysis.

1.2.2.2 Study characteristics

We found three studies: two randomized controlled trials and one prospective observational study

i) Description of the included studies

The table explains the available evidence on the clinical effectiveness of the device:

Table: 7 Clinical Effectiveness

Study Details	Study Design	Target Group	Outcome Measure	Summary of findings
Dawson et al. (2011), Australia [51]	Randomized Controlled Trial	preterm infants requiring ventilation	SpO2, Use of CPAP, Endotracheal Intubation	No significant difference between the median SpO2 in the T-piece and SIB groups, no difference in the groups in use of CPAP, endotracheal intubation, or administration of surfactant in the delivery room
Thakur et al. (2014), India [52]	Randomized Controlled Trial	preterm infants requiring ventilation	duration of PPV, intubation rate	The median (Interquartile range) duration of PPV significantly less for ARD device vis a vis Self inflating bag, higher intubation rates for SIB neonates vis a vis ARD Device
Guinsburg et al. (2017), Brazil [35]	Pragmatic prospective cohort study	preterm infants requiring ventilation	Survival to hospital discharge without Bronchopulmonary Dysplasia (BPL), grade IV Intraventricular haemorrhage and periventricular leucomalacia	ARD Device increased the chance of survival to hospital discharge without major morbidities.

ii) Study quality assessment

The name of the journals in which these studies were published are tabulated in the following table:

Author	Journal	Impact Factor	H-index
Thakur et al. (2014), India [52]	Resuscitation	4.572	123
Dawson et al. (2011), Australia [51]	Journal of Pediatrics	3.890	188
Guinsburg et al. (2017), Brazil [35]	BMJ	27.604	392

Guinsburg et al. is a prospective observational study, but the possible bias of the observational study has been addressed via prospective score matching in the study. They found that "After adjusting for maternal morbidity, antenatal steroid use, delivery mode, gestational age, sex of the new-born and first minute Apgar score, ventilation with the T-piece at birth was associated with an increased chance of fifth-minute Apgar score of 7–10 by 37%, suggesting that this device provides more effective ventilation for resuscitation in the delivery room" [35].

1.3 Meta-analysis of the evidence:

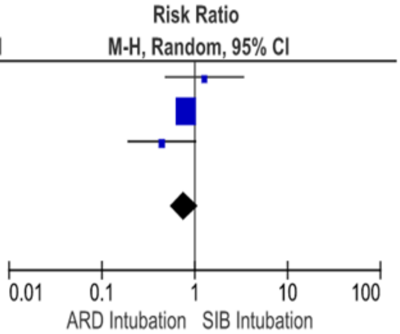
Using the clinical evidence from the above table, we developed forest plots for the risk ratio for the mortality rate and the intubation rate.

As per this evidence, the rate of intubation when using ARD reduces by 23% when compared to SIB, and the rate of mortality reduces by 40% when using ARD vis a vis SIB.

Figure:7 Forest Plot for Intubation Rate

Study or Subgroup	ARD Intubation Events	ARD Intubation Total	SIB Intubation Events	SIB Intubation Total	Weight	Risk Ratio M-H, Random, 95% CI
Dawson 2011	8	41	6	39	11.7%	1.27 [0.48, 3.32]
Guinberg 2017	782	1456	340	506	73.3%	0.80 [0.74, 0.86]
Thakur 2015	6	40	17	50	14.9%	0.44 [0.19, 1.01]
Total (95% CI)		**1537**		**595**	**100.0%**	**0.77 [0.54, 1.11]**
Total events	796		363			

Heterogeneity: Tau² = 0.04; Chi² = 2.85, df = 2 (P = 0.24); I² = 30%
Test for overall effect: Z = 1.41 (P = 0.16)

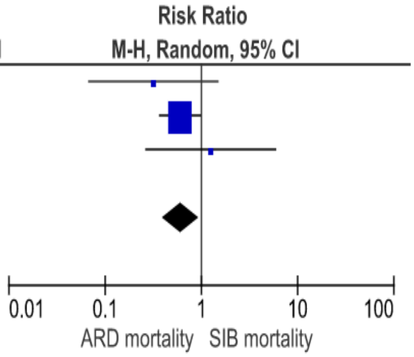


Mortality reduces by 40% when using ARD vis a vis SIB.

Figure:8 Forest Plot for Mortality Rate

Study or Subgroup	ARD mortality Events	ARD mortality Total	SIB mortality Events	SIB mortality Total	Weight	Risk Ratio M-H, Random, 95% CI
Dawson 2011	2	41	6	39	8.2%	0.32 [0.07, 1.48]
Guinburg 2017	43	1456	25	506	83.6%	0.60 [0.37, 0.97]
Thakur 2015	3	40	3	50	8.2%	1.25 [0.27, 5.86]
Total (95% CI)		**1537**		**595**	**100.0%**	**0.60 [0.39, 0.94]**
Total events	48		34			

Heterogeneity: Tau² = 0.00; Chi² = 1.53, df = 2 (P = 0.47); I² = 0%
Test for overall effect: Z = 2.25 (P = 0.02)



1.4 Operational Challenges while handling these devices

We conducted a survey to assess the Operational Challenges between ARD and SIB. We presented a questionnaire with device usage related, staff related and maintenance related questions to the nurses and the doctors to two tertiary level public hospitals and seven tertiary level private hospitals in Vishakhapatnam and one tertiary level public hospital in Guntur. The questionnaire has been added in the appendix for reference. The questions ranged from which device is being used in NICU, and the learning methodology to ease of use, maintenance and adverse events.

One of the respondents had been using T-Piece resuscitator, while the other respondents had been using SIB. The user had been using T-Piece resuscitator for over a period of two years, and depending on the ease of use and features such as ability to variate the PEEP, he found the device user-friendly for handling neonates with birth asphyxia. The challenges mentioned by the user while operating the device was the entailing training cost, and the need of centralized oxygen supply to operate the device. The user had recently switched to T-Piece with blender, which has the flexibility of varying FiO_2, and he told us that it was an effective move for the very low birth weight neonates who needed FiO_2 in the range of 20-30%. However, the incremental cost for adding the blender to a regular T-Piece was high (Rs 80,000+), and hence it might not be a cost-effective intervention in the public healthcare setting.

All the other hospitals had been using SIB as the standard of care for more than a year. The number of staff required for using this device ranged from 1-3 mostly except for one hospital which engaged an entire Cardio-Pulmonary Resuscitation (CPR) team for the resuscitation exercise. All the respondents said that the device is user friendly, and it took 0-2 minutes to initiate treatment with the device. The device rarely broke down in the experience of all the respondents.

One of the respondents had purchased a T-Piece resuscitator two years ago, but he was averse to use it in a clinical setting, and used it only for demonstration purposes. When asked about the underlying reasons the respondent mentioned that the standard of care was safe and effective enough and there wasn't a need to switch to a new device.

Surprisingly, the other respondents didn't have any knowledge about the T-piece resuscitator. However, when informed about this device, some respondents gave their feedback on it such as:

- The T-Piece resuscitator's adjustable Positive end-expiratory pressure (PEEP) might improve outcomes and reduce the ventilation rates. This would also reduce the hyperventilation rates caused by the use of SIBs.
- One respondent was sceptic about the Automated function of the TPR device and the inability to control Volume and pressure as per the requirement of the doctor.

A recent bench study by Guinsburg et al. (2019) [63] supports this scepticism as "The most important and somewhat frightening result is the significant inadvertent PEEP levels delivered by the devices with airway pressure limit valves when infant lung models with high compliance were evaluated. At the same time, some of these devices, specifically two inbuilt

T-piece resuscitator systems, also delivered higher than expected PIP in infant lung models with low compliance.”.

However, the authors also mention the fact that we need a randomized clinical trial in order to verify this phenomenon.

The following figures summarize the findings

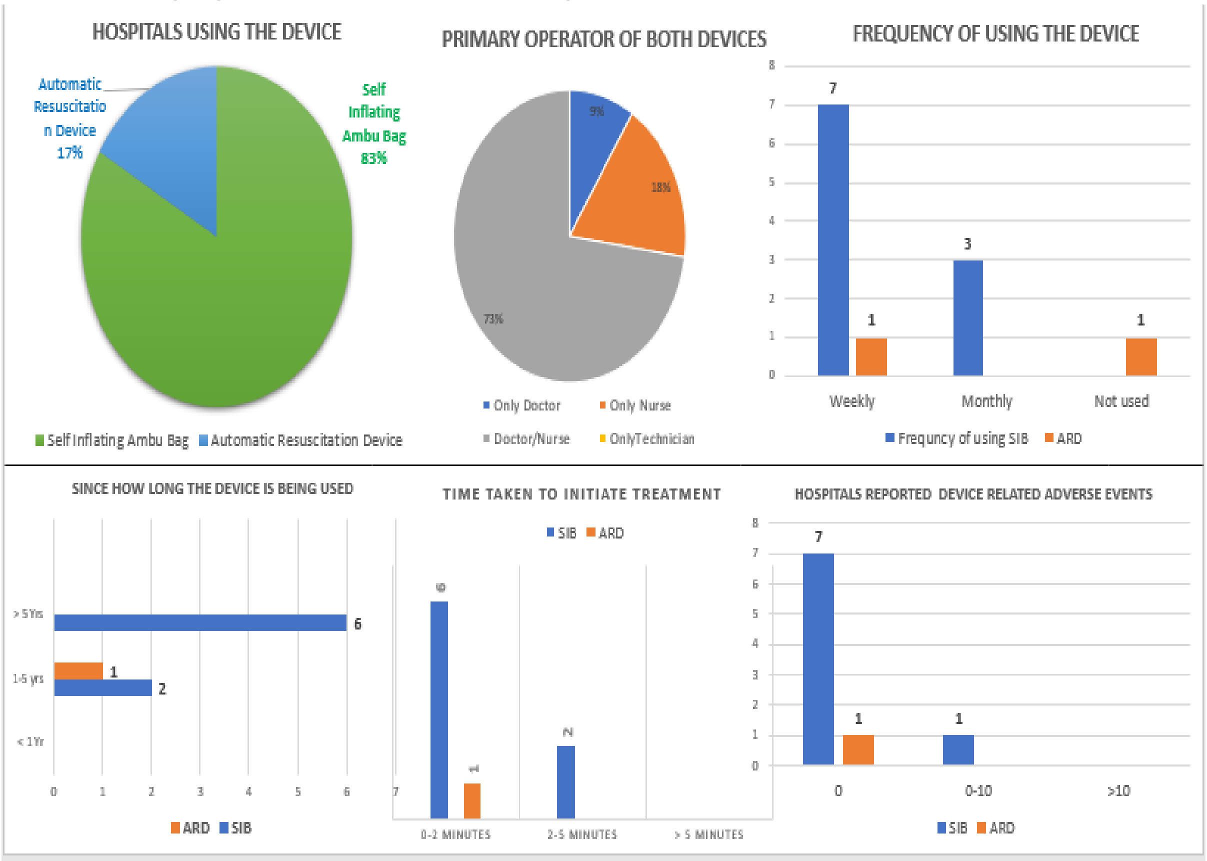


Figure:9 Summary Findings- Operational Challenges

Chapter 3. Economic Evaluation of the Automated Resuscitator Device

3.0 Introduction

We calculate the Cost-Effectiveness of the Automated Resuscitator Device vis a vis Self Inflating Bag. We compare the cost of both the interventions from a societal perspective, and the used Disability Adjusted Life Years to measure the economic burden.

The PICO parameters as per the intervention were defined as following:

Population	Birth asphyxiated new-borns requiring resuscitation in Public health care settings.
Intervention	Automated Resuscitation Device (type of T-piece resuscitator)
Comparators	Self-inflating bag
Outcome	Primary Outcome: - Cost Effectiveness measure: Incremental cost effectiveness ratio (ICER) - Disability Adjusted Life Years (DALYs) Secondary Outcome: - Intubation rate - Mortality rate
Time horizon	Lifetime
Perspective	Societal

We used DALYs to measure the economic burden following reasons:

- Definition of DALY: One DALY can be thought of as one lost year of "healthy" life (WHO).
- DALYs for a disease or health condition are calculated as the sum of the Years of Life Lost (YLL) due to premature mortality in the population and the Years Lost due to Disability (YLD) for people living with the health condition or its consequences. In neonatal resuscitation patients, premature mortality is the main problem and disability due to a number of reasons is also important as highlighted before.[36]
- EQ-5D has been derived from adult scores. For neo-nates there is no accepted EQ-5D methodology.

3.1 Cost-Effectiveness Analysis

3.1.1 Decision Tree

We built a de-novo mathematical decision model will be built to assess the comparative cost-effectiveness of Automated Resuscitation Device versus Self-inflating bag.

We used MS-Excel to build a decision analytic model to compare a New Automated Resuscitated Device (T-Piece resuscitator) with Self-inflating bags, which is the most commonly used method for resuscitation.

- The decision tree model begins with a decision node: Neonates requiring resuscitation,
- The next nodes are resuscitation with the NARD device and resuscitation with self-inflating bag. The next level are chance nodes for survival vs death with these resuscitators. The next chance node in the decision tree had three outcomes among survivors: Survival with BPD (Bronchopulmonary dysplasia), IVH (Intraventricular Haemorrhage) grade III/IV or PVL (Periventricular Malacia), Survival without BPD and Survival without BPD, IVH (III/IV) or PVL[35].

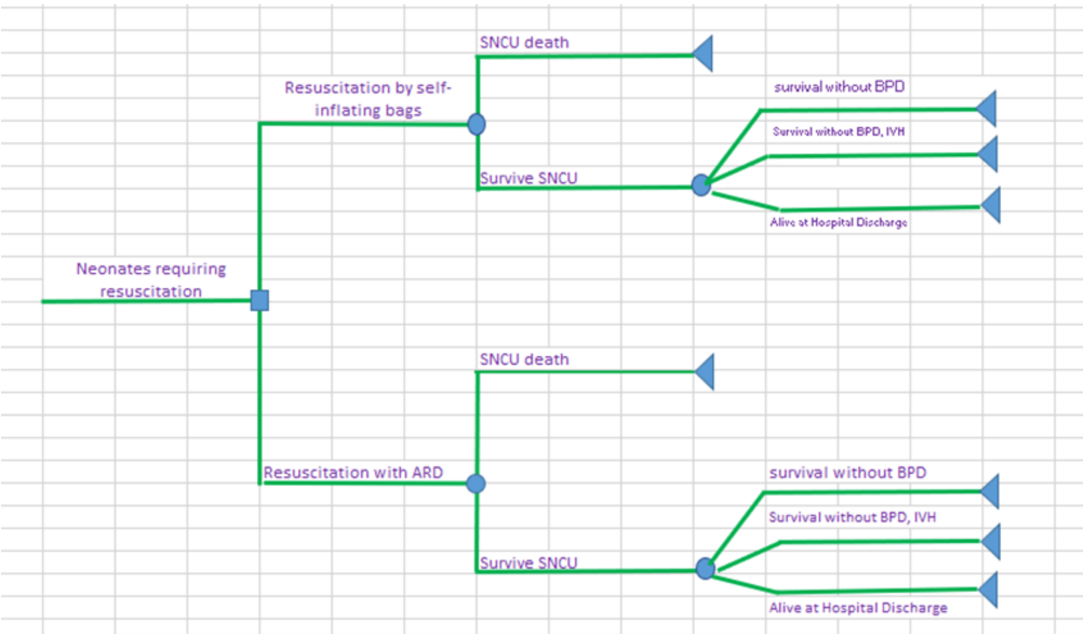


Fig. 10. Decision Tree

3.1.2 Sample and Probabilities

We used the pragmatic prospective cohort study data from Guinsburg et al. (2017)[35] to estimate the annual transition probabilities of a neonate requiring resuscitations. The follow up period in the study was 27 days, and all these probabilities were calculated for a 27 day period. In this study 1456 (74%) neo-nates were ventilated with T-piece resuscitator and 506 (26%) with the self-inflating bag.

3.1.3 Outcome Status

We classified neonatal outcomes among survivors into three groups: (1) Survival with BPD (Bronchopulmonary dysplasia), IVH (Intraventricular Haemorrhage) grade III/IV or PVL (Periventricular Malacia) (Severe), (2) Survival without BPD (Moderate) and (3) Survival without BPD, IVH (III/IV) or PVL[1]. (Mild/Normal). Due to lack of availability of direct outcomes, we took these three as surrogate outcomes [53].

The transition probabilities are tabulated here:

Transition Probabilities	Values
Probability of dying after being treated with T-piece	0.03
Probability of dying for infants after treated with self-inflating bags	0.05
Probability of developing severe disability after being treated with T-piece	0.004
Probability of developing moderate impairment after being treated with T-piece	0.525
Probability of developing mild/ no disability in infants after treated with T-piece	0.471
Probability of developing severe disability after being treated with self-inflating bags	0.257
Probability of developing moderate impairment after being treated with self-inflating bags	0.391
Probability of developing mild/no disability in infants after treated with self-inflating bags	0.352

[1] Guinsburg et al.2017

Secondary Outcomes:

Probability of Intubation with SIB	0.67
Probability of Intubation with ARD	0.54

The data for long term disability free survival was not available.

3.1.4 Disability Adjusted Life Years

As per the World Health Organization (WHO)- "One DALY can be thought of as one lost year of "healthy" life"[2]. DALYs for a disease or health condition is the sum of Years of Life lost (YLL) due to premature mortality in the population and the Years Lost due to Disability (YLD).

As mentioned earlier we used DALYs as the outcome for to measure the burden of the disease as there was a lack of Quality Adjusted Life Years (QALYs) data for neonates born with asphyxia. The EQ-5D used for calculating the QALYs has been derived from adult scores. For neo-nates there is no accepted EQ-5D methodology.

In order to calculate DALYs, we used the discrete time approach developed by Larson 2013[54]. The discount rate was assumed to be 3%, and the life expectancy for Andhra Pradesh calculated using the Life tables issued by the Census Bureau of India.

The unfortunate death of a neonate leads to a loss of 69.6 years of life lost [Average life expectancy in Andhra Pradesh during the time period 2013-17 as per the Census Bureau of India[55]]. For the neonates who survive with severe/mild and moderate asphyxia, we use the disability weights extracted from the Global Burden of Disease 2017 report [36]. We assumed that all the neonates who survive with disability get to live through the entire life span of 69.6 years.

Table: 8 Disability Adjusted Life Years

	Disability Weight	Discounted DALYs
Death	1	29.94508948
Survival with Severe Disability	0.402	12.03792597
Survival with Moderate Disability	0.061	1.826650458
Survival with mild/no disability	0.01	0.299450895

[2]Metrics: Disability-Adjusted Life Year (DALY) - WHO

4. Costing

We have used Time Driven Activity Based Costing (TDABC) approach developed by Kaplan and Anderson [39] for costing the per patient cost for neonates born with asphyxia who undergo resuscitation through Self-inflating bag and the Automated Resuscitator Device. It is a bottom-up accounting method which needs two parameters: the quantity of time (capacity) the patient uses of each resource at each process and capacity cost rate for each resource [40]. This approach helps in assigning costs accurately to each process along the path. TDABC approach can help in determining costs in the setting of bundled payments [41] as well as act as a useful tool to allocate resources in the most effective manner with minimum wastage [42].

In order to implement TDABC, we have used data from secondary research. We began by developing process maps for neonates who undergo Non-invasive ventilation using standard treatment protocol issued by the WHO for the management of asphyxiated new-born to account for the treatment and services provided [43]. We tried to assign accurate costs to all the individual processes along the path of treatment using this approach.

We have segregated costs into three components: personel, equipment and overhead. We calculated the personel costs using the TDABC approach for the staff (doctors and nurses), this data was collected by secondary study. We used the UNICEF rate [44] list to calculate equipment costs, find factors such as the depreciation rate of the equipment, space occupied, cost of utilities and consumable supplies associated with the equipment, its maintenance and repair costs using secondary data, and allocate these equipment costs to the stages in the process maps.

4.1 Process Mapping of Asphyxiated Neonatal Care using TPR and SIB's

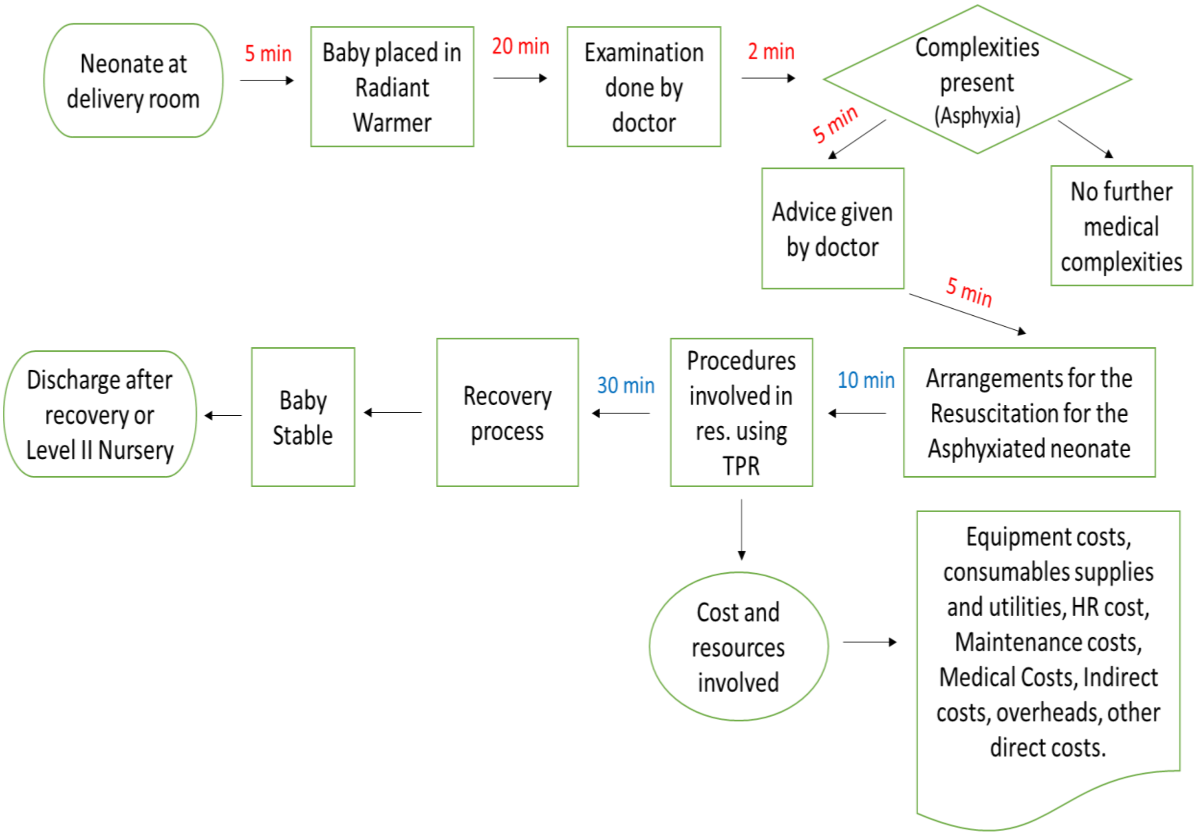


Fig. 11. Process mapping neonatal care in the delivery room using TPR.

The above process map depicts the steps involved in the neonatal care in the delivery room using TPR. We start the process mapping with neonate in the delivery room after its birth. The time frame for the movement of neonate to radiant warmer (including the arrangement of radiant warmer) has been taken as 5 minutes) [45]. After the baby is placed in the radiant warmer the doctor does the examination, which includes all the tests concerning the basic health state of a neonate, this also includes the Apgar score. The time frame is 20 minutes. The next step in the examination is checking whether the neonate is suffering from asphyxia or not, time duration for this is 5 minutes. Once the doctor finds that neonate is not suffering from asphyxia and other diseases than there are no further medical complications. If a neonate is suffering from asphyxia than the doctor gives the advice, which will be followed by the arrangements of resuscitation process of a neonate. The time duration for both the activities is taken as 5 minutes each. The arrangement process is assisted by the nurses and mid wives. This involves seven-step setup procedure [47] after which the neonate is given resuscitation. The total time we have assumed for this is 40 minutes.

Through the primary survey we found that for the functioning of the T-Piece Resuscitator we require one doctor/ paediatrician and two nurses.

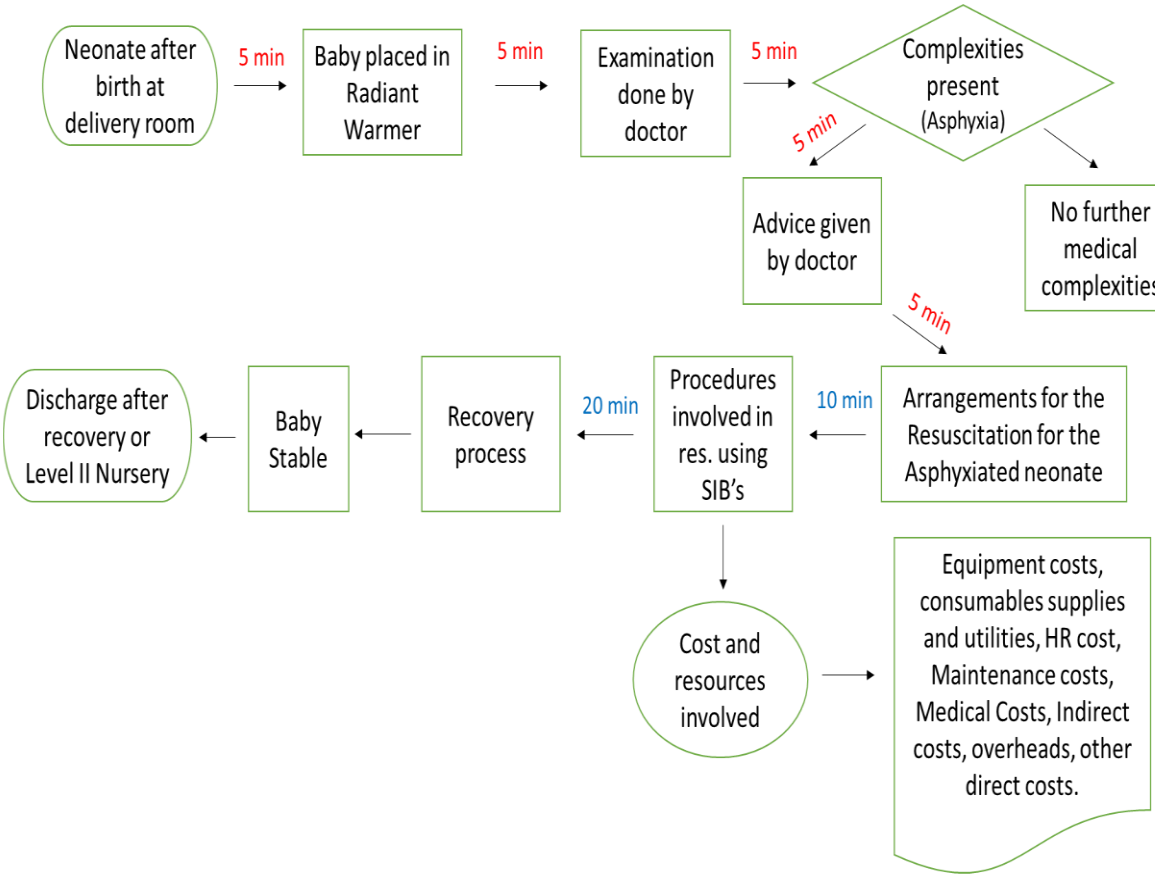


Fig. 12. Process mapping neonatal care in the delivery room using SIB's

The process map of using self-inflating bag as described in figure 13 is almost similar to the explained TPR process map. The slight variation between the two is that self-inflating bag it is a simple ready-to-use device, whereas the Neopuff requires seven steps to be followed prior to its operation [47]. Based on this we have made an assumption of less time requirement which is 20 minutes plus 10 minutes, a total of 30 minutes. Even the cost of operation of SIB's is relatively cheaper than the TPR because it does not consume power, space cost and maintenance cost is negligible. The cost involved in consumable supplies and overheads is relatively lesser than the TPR. For the Labour cost, we found that the requirement of labour will be less for SIB's because of simple procedure and less skill requirement as compared to the TPR. We have assumed the requirement as one doctor or paediatrician and one nurse. Other steps remain the same which is recovery process where baby comes to a stable state, which is followed by discharge of neonate after the recovery.

4.2 Equipment and Labor Cost

3.2.1 Market Prices for the devices

Table: 9 Cost of ARD

Equipment	Price	Sources
ARD	₹ 46300	Kerala medical services corporation ltd (KMSCL)
Consumable Supplies:		(KMSCL)
1. Disposable infant resuscitation T piece circuit	₹ 45 per unit	www.indiamart.com
2. Disposable infant resuscitation T piece mask	₹ 450 per unit	www.indiamart.com
3. Disposable humidifier T-piece circuit with heated wire	₹ 2000 per unit	www.indiamart.com
Annual / Comprehensive Maintenance Charges		
1. Labor	₹ 500	KMSCL
2. Comprehensive	₹ 600	KMSCL
Total	₹ 600	
Depreciation cost percent	13%	Prinja et al.
Overheads:		
1. Training Costs		--------
2. Other Costs		--------
Total Cost for ARD	**₹ 49,560.00**	

Table: 10 Cost of SIB

Equipment	Price	Sources
Self-Inflating Bags (SIB's)	Rs. 3000	www.indiamart.com
Depreciation cost percent	13%	Prinja et al.
Consumable Supplies:		
1. Neonatal Mask	₹. 349 per unit	www.amazon.in
Maintenance Costs:		--------
1. Sterilization Costs		--------
2. Other Costs		--------
Total Cost for SIB	**₹ 3,422.00**	

3.2.2 Labor Cost

The labor cost has been calculated using the Time driven activity based costing approach:

Table: 11 Labor cost in the resuscitation process

Equipment	**Time spent per neonate (in min.)**	**No. of Staffs (Nurse)**	**No. of Staffs (Pediatrician)**	**Costs per min. (Nurse)**	**Costs per min. (Pediatrician)**	**Total cost per neonate**
ARD	30 min	2	1	Rs. 2.73	Rs. 14.31	Rs. 593
SIB	20 min	1	1	Rs. 2.73	Rs. 14.31	Rs. 341

The following calculation in the above table is done on the fact that the salary of nursing staff and pediatrician who are involved in the resuscitation process is Rs163.8 per hour for nurse and 859 per hour for the pediatrician (www.glassdoorco.in). We evaluated that the labor cost for every single neonatal resuscitation as Rs. 593 and Rs. 341 for TPR and SIB's respectively. The Cost per minute or the capacity cost is Rs. 2.73 for nurse and Rs. 1431 for pediatrician. The rationale behind keeping more time and more no. of staff (nurse) for TPR as compared to SIB's is that SIB's is comparatively easier to function, and two nurse or pediatricians can comfortably operate it. TPR it is more complex than SIB's, more time and skilled personal is required for carrying resuscitation using the TPR. TPR is more complex can be justified from the fact that there are seven steps for setting up the resuscitation procedure [47].

4.2.3.Per Patient Cost of Resuscitation:

In order to calculate the cost of assets, we have assumed that the life of each fixed asset is 5 years, and the discount rate is 3%. The maintenance cost is assumed to be 8%. As assumed earlier, we would carry on the assumptions of per patient time as 30 minutes for the T-piece resuscitator. We have assumed 8 working hours with 100% utilization i.e. 2 neonates undergo resuscitation every hour. These assumptions are subject to change as we gather more data on this procedure.

The other equipment besides T-Piece and SIB were identified using the UNICEF rate list [48].

The total cost of fixed assets per patient was calculated based on these assumptions. We calculated the per patient consumables from the UNICEF list as well.

The results for resuscitation through ARD and SIB are tabulated in the following tables:

Table: 12 Cost per patient- Resuscitation through ARD

Labor Cost per patient	593
Fixed Assets per Patient	13.53712344
Cosumables per patient	3590.85
Total Cost per patient	4197.387123

Table: 13 Cost per patient- Resuscitation through SIB

Labor Cost per patient	341
Fixed Assets per Patient	7.69827169
Cosumables per patient	1444.85
Total Cost per patient	1452.548272

4.3 Costing from Societal Perspective

We add the out of pocket expenditures (OOPE) data from a NHSRC report about Household Healthcare Utilization &Expenditure in India: State Fact Sheets,2014 [49].

Inflation adjusted (as per the Consumer Price Index[3] data) figures for public hospitals in Andhra Pradesh are given in the following table:

Table: 14 Out of Pocket Expenses

	2014	2019
OOPE per birth child-Rural	1452	1696
OOPE per birth child-Urban	1232	1438

For our analysis, we used the OOPE for the Rural Households.

4.4 Cost of NICU bed

We calculated the per day cost of stay in NICU from Prinja et al. [66]. The authors in this study used bottom-up approach to account for the health system resources such as capital, equipment, drugs and consumables, non-consumables, referral and overheads utilized to treat all neonates.

The authors use this approach to find out the per bed day cost from societal perspective in level II neonatal hospitals in four district hospitals in three states of India: Shivpuri and Guna (Madhya Pradesh), Bhubaneshwar (Orissa) and Vaishali (Bihar). We took data from Vaishali in our analysis. In order to calculate the median stay of the neonates in NICU, we took data from Narang et al [50]. Depending upon the level of severity of the neonate as defined in the following, the authors calculated the median stay in the hospital for a neonate. The 2010 figures were adjusted for inflation[4].

Severe	Weight <1000g
Moderate	1000<Weight<1250g
Mild	Weight>1250g

Table 15: Cost of NICU Bed (Level II Hospitals)

	Median Days in NICU	Per day Cost(Societal) 2010	Per day cost (societal) 2019	Total Societal Cost 2019
Severe	28	2752	4477.425976	125367.9273
Moderate	14	2752	4477.425976	62683.96367
Mild	7	2752	4477.425976	31341.98184

[3] https://www.inflation.eu/inflation-rates/india/historic-inflation/cpi-inflation-india.aspx

[4] ibid

5.Results

After putting these values in the decision tree, we obtained the following results:

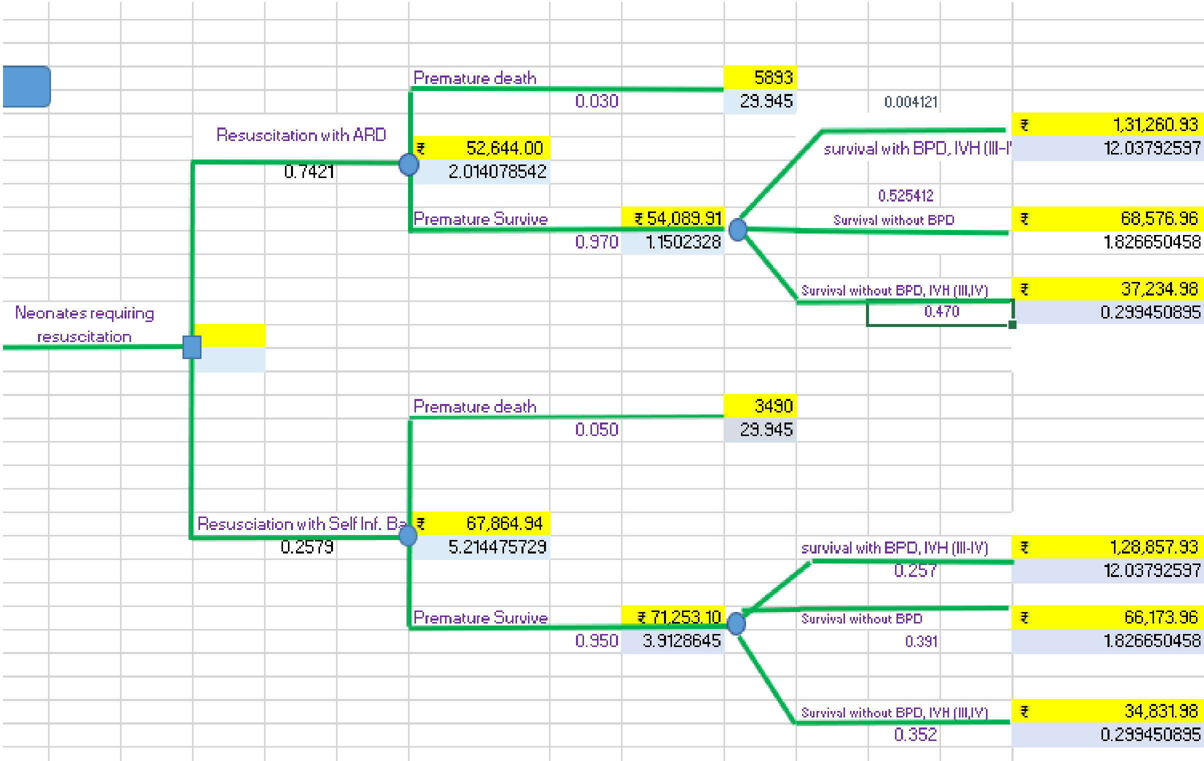
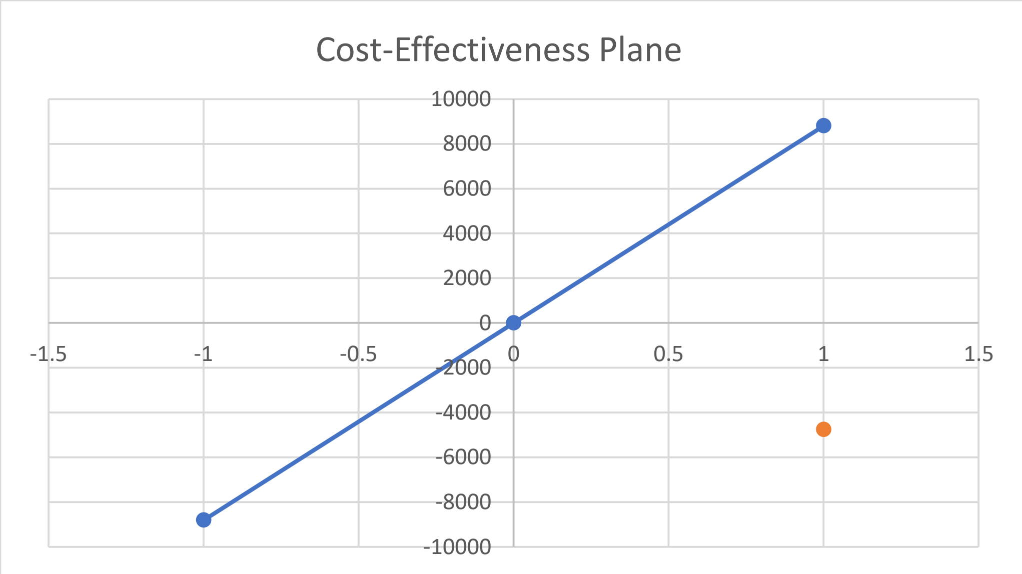


Fig. 13. Decision Tree Results

Table:16 ICER

Cost SIB	67864.94411
Cost ARD	52644.00028
DALY SIB	5.214476
DALY ARD	2.014079
ICER	-4755.95

Figure 14: Cost-Effectiveness Plane



The Incremental Cost Effectiveness Ratio is -4755.95 per DALY averted for the ARD device. The negative value in red in the above graph clearly implies that the intervention is cost-effective. The Willingness to pay threshold was taken as GDP per capita per month for India[5]. (Rs 8807.33)[6]. We run One-way sensitivity and probabilistic sensitivity analysis to check for the robustness our analysis to various structural, model and parameter uncertainties.

6.One Way Sensitivity Analysis

The One-Way Sensitivity Analysis was done to assess the robustness of the model to deterministic parametric uncertainty. The lower and upper bounds were taken as twenty percent of the base case values for all the parameters.

As this graph suggests, the ICER is most sensitive to the probability of severe disabilities when SIB is used.

[5] Source- PRESS NOTE ON PROVISIONAL ESTIMATES OF ANNUAL NATIONAL INCOME, 2018-19 AND QUARTERLY ESTIMATES OF GROSS DOMESTIC PRODUCT FOR THE FOURTH QUARTER (Q4) OF 2018-19, NSO, Ministry of Statistics and program implementation, Government of India

[6]The WHO-CHOICE criteria for the threshold is GDP per capita/DALY Averted for a developing country

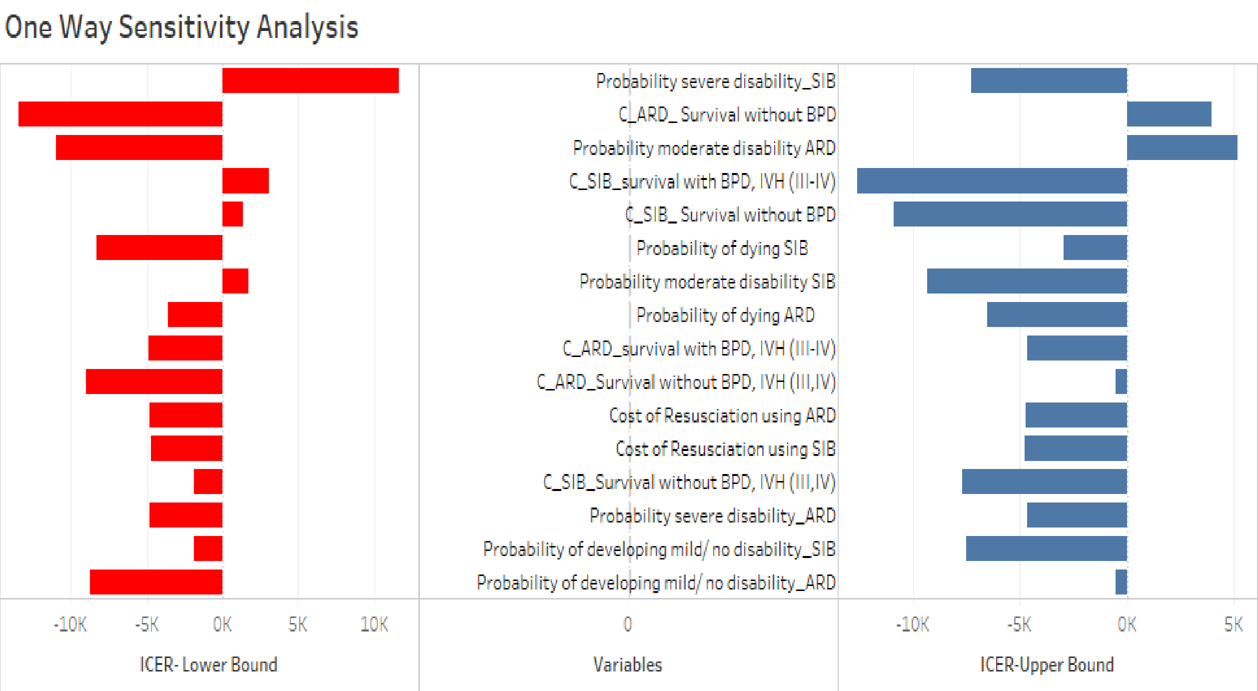


Fig. 15. One Way Sensitivity Analysis Results

7.Probabilistic Sensitivity Analysis

We ran Monte carlo simulations to assess test the robustness of our analysis to various structural, model and parameter uncertainties. For probability distributions we assumed beta distribution, and for cost data we assumed gamma distribution. We ran 1000 simulations to obtain the following results:

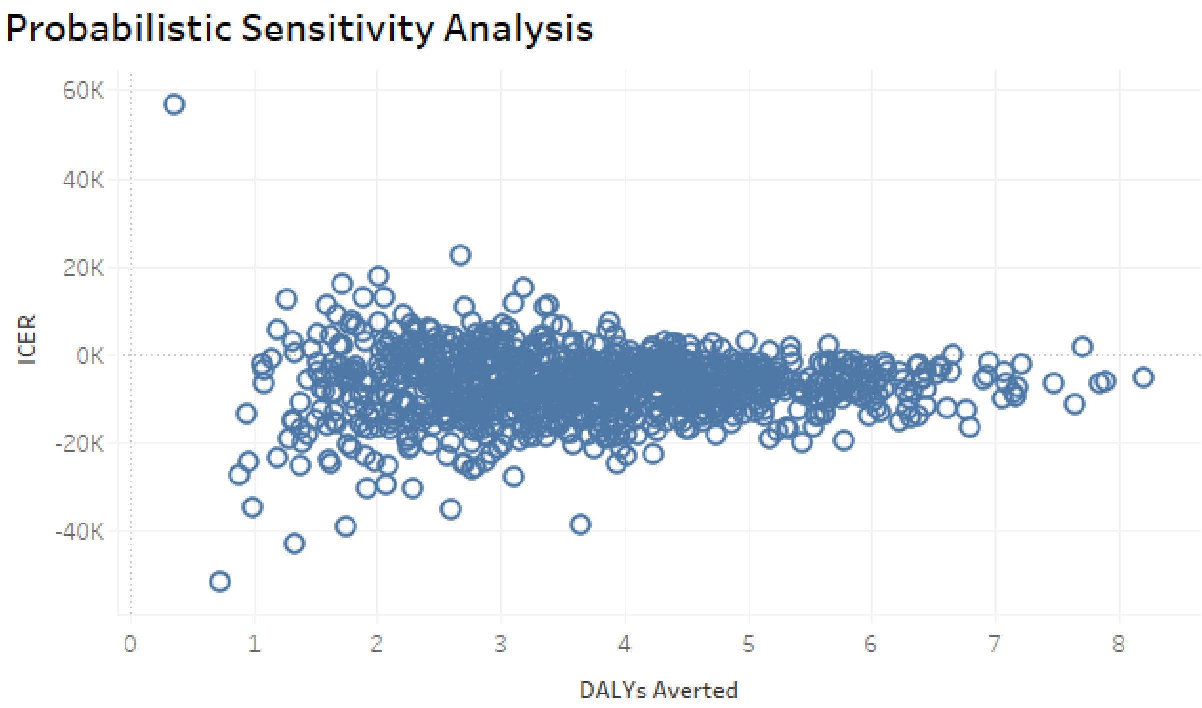


Fig. 16. Probabilistic Sensitivity Analysis

8.Cost Effectiveness Acceptability Curve

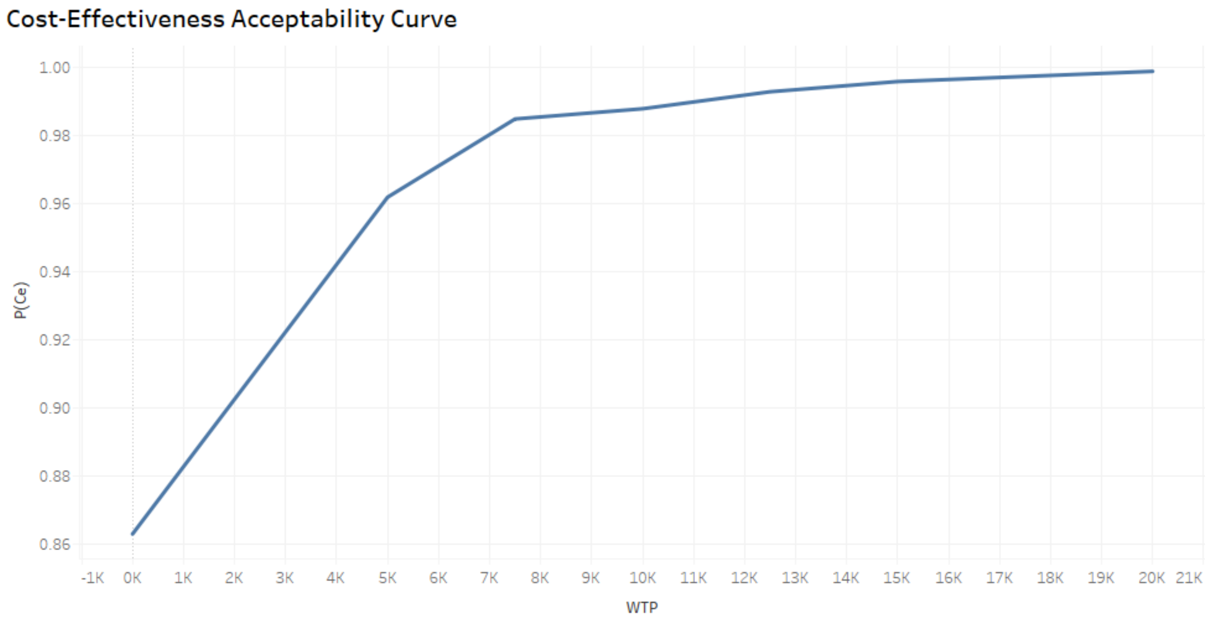


Fig. 17. Cost-Effectiveness Acceptability Curve

We obtained the following cost-effectiveness acceptability plot based on the PSA simulations. We observe a 95% probability of Cost-effectiveness with a Rs 5,000/- threshold.

9. Budget Impact Modelling for the high burden states in India

Indian states Madhya Pradesh, Odisha, Uttar Pradesh, Uttarakhand and Rajasthan have the highest neo-natal mortality rates in India [56]. We have made a Budget Impact model to see the impact of implementation of ARD in public healthcare setting from the provider's perspective.

We assume a 100% utilization rate and the following market share proportion for ARD when compared to SIB for this analysis:

	2020	**2021**	**2022**	**2023**	**2024**
SIB (SoC)	90%	80%	60%	50%	40%
ARD	10%	20%	40%	50%	60%

We compare the above scenario to the scenario under which all the asphyxiated newborns are still treated with the Self Inflating Bag for the next five years.

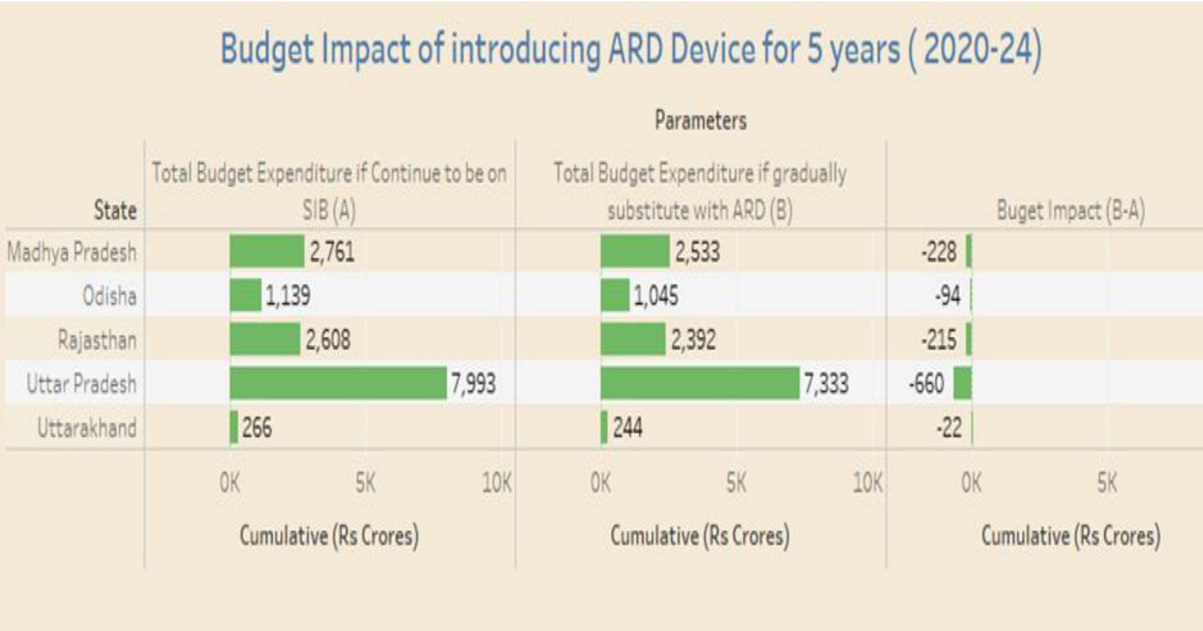
In order to estimate the number of deliveries per year for these years, we assumed that the proportion of number of deliveries to the overall population of the state remains constant throughout these five years. To calculate this proportion, we used the state wise data on number of deliveries in a state for the year 2015 (latest available data) from the NHSRC Database[57], and divided it by the total population in the year 2015 of this state. Using this rate, we estimated the number of expected deliveries in a state for the years 2020-24. The population and the growth rate were estimated from the Census Bureau of India data [55].

We took the incidence rate as 3.63% as per the chapter 1 of this report to estimate the number of asphyxiated neonates each year. Then using the per patient cost we obtained for both ARD and SIB, we estimate the budget impact for all these five states.

As per the analysis, even though per patient cost for ARD is higher than SIB, the reduction in severe cases leads to an overall cost-saving when the exchequers move towards higher ARD take up in the treatment mix due to the reduction in number of severe cases.

The calculations are shown in the appendix. If the incidence rates for asphyxia and for the severe, moderate and mild cases remain the same as inferred from the literature, the gradual take up of ARD would lead to cost-saving of Rs 660 Crores in Uttar Pradesh, 94 Crores in Orissa, 215 Crores in Rajasthan, 228 Crores in Madhya Pradesh and 22 Crores in Uttarakhand respectively.

Figure: 18 Budget Impact modelling results



10.Conclusion

We conducted a systematic review on the evidence of clinical effectiveness of the ARD. The evidence on clinical effectiveness is limited, but it does indicate that this device reduces the severe cases caused due to birth asphyxia, and it reduces both intubation and mortality rate for neonates who suffer from birth asphyxia at the point of delivery.

We also conducted a survey to find the operational challenges the practitioners face while using this device. The features such as automation of PIP and ability to vary PEEP were considered user friendly for critical care by the respondents using ARD.

We designed process maps and collected data for the cost at the secondary level neonatal intensive care units, and we calculated disability adjusted life years (DALYs) for both the interventions. The Incremental Cost Effectiveness ratio (ICER) for the new device when compared to self-inflating bag is -4755.95 Rs/DALY averted. The negative ICER value implies that the new device is both clinically and cost effective compared to the standard of care.

In order to check the robustness of these results, we ran Monte carlo simulations and found that new device would be cost-effective with 95% probability at Rs 5,000/-. The ICER is most sensitive to the probability of severe cases for neonates treated with the standard of care.

11. Limitations

We did not include the cost of the blender into consideration. As mentioned in the operational challenges section that even though the use of blender would provide the possibility of varying FiO2. But with the incremental cost of adding this is high and with the lack of enough evidence on the need of such a device, it might not be a cost-effective intervention. As one of the studies has found that the stabilization/resuscitation of VLBW infants can be initiated with an FiO2 of less than 100% and even with room air without concomitant early overt morbidity.[67]

We have not included the training costs into consideration. Usage of this device would require 2-3 days of modular training.

Lastly, the evidence we have synthesized for clinical effectiveness is limited as we have only two randomized controlled trials and one prospective observational study. We found only one medical practitioner was using this device, hence we might need to collect more data on clinical effectiveness, ease of use and operational challenges.

12. Final Recommendation

Based on the Incremental Cost Effectiveness ratio value we obtained, the ARD device reduces both the cost and averts Disability adjusted life years by the virtue of reducing the number of severe cases caused due to birth asphyxia. Based on this analysis, the device can be used at a tertiary level healthcare setting.

However, this study has some limitations which need to be addressed before making this decision as the clinical effectiveness data used in this report was taken from a prospective observational study done in Brazil, and secondly, the data for costing was taken from secondary sources. We recommend a pilot study based in India in order to collect more accurate data on the clinical and cost effectiveness in Indian healthcare setting.

Appendix 1: Search Strategy for Systematic Review on Incidence and prevalence of neonates with birth Asphyxia below 28 days in India

Pubmed search strategy

1	**((((neonates) OR infants) AND children) OR child) OR kids**	2198245
3	**(((mortality) OR death) OR dying) OR lethality**	1787072
4	**(((morbidity) OR depression) OR vexation) OR dullness**	415721
5	**(((incidence) OR rate) OR number**	440393
6	**(((prevalence) OR popularity OR ubiquity**	2594175
7	**(((((neonates OR infants OR children OR child)) AND (asphyxia OR suffocation OR breathless)) AND (Mortality OR death OR dying OR lethality)) AND (Morbidity OR depression OR vexation) AND dullness(((incidence) OR rate) OR number(((incidence) OR rate) OR number**	2393

	AND (((prevalence) OR popularity OR ubiquity	

Appendix: 2 Cochrane search strategy

1	**neonates):ti,ab,kw OR (infants):ti,ab,kw OR (children):ti,ab,kw OR (child):ti,ab,kw OR (kid):ti,ab,kw**	154621
2	**((asphyxia):ti,ab,kw OR (suffocation):ti,ab,kw OR (breathless):ti,ab,kw**	1013
3	**(mortality):ti,ab,kw OR (death):ti,ab,kw OR (dying):ti,ab,kw OR (lethality in india):ti,ab,kw**	120270
4	**morbidity):ti,ab,kw OR (depression):ti,ab,kw OR (vexation):ti,ab,kw OR (dullness):ti,ab,kw**	100234
5	**incidence in india):ti,ab,kw OR (rate):ti,ab,kw AND (number):ti,ab,kw**	42535
6	**prevalence):ti,ab,kw OR (ubiquity):ti,ab,kw OR (popularity):ti,ab,kw**	34997
7	**(neonates OR infants OR children OR child OR kids):ti,ab,kw AND (asphyxia OR suffocation OR breathless):ti,ab,kw AND (Morbidity OR death OR dying OR lethality):ti,ab,kw AND (morbidity OR vexation OR depression OR dullness):ti,ab,kw AND (Incidence OR Rate OR number):ti,ab,kw**	42
8	**((Morbidity OR death OR dying OR lethality) AND (morbidity OR vexation OR depression OR dullness) AND (Incidence OR Rate OR number)):ti,ab,kw AND**	1267

	(prevalence OR ubiquity OR Popularity in india):ti,ab,kw	

Appendix: 3

Google scholar search strategy: 5346.

Appendix 2 Search Strategy for Systematic Review on the Clinical Effectiveness of the device

Appendix

Pubmed search strategy

1	**((((Neonates) OR infants) AND children) OR child) OR kids**	**2198245**
2	**((((neonates) OR infants) OR children) AND birth asphyxia) OR suffocation**	**20409**
3	**(((t piece resuscitation)**	**94**
4	**(((Self inflating bag)**	**187**
5	**(((((neonates) OR infants) OR children) AND birth asphyxia) OR suffocation) AND t-piece resuscitation OR self-inflating bag**	**9**

Appendix: 2 Cochrane search strategy

1	**neonates):ti,ab,kw OR (infants):ti,ab,kw OR (children)**	**166744**
2	**((asphyxia):ti,ab,kw OR (suffocation):ti,ab,kw OR**	**1013**
3	**((t piece resuscitation)**	**72**
4	**((Self inflating bag)**	**59**
5	**(((((neonates) ti,ab,kw OR infants) ti,ab,kw OR children) ti,ab,kw AND birth asphyxia) ti,ab,kw OR suffocation) ti,ab,kw AND t-piece resuscitation ti,ab,kw OR self inflating bag**	**72**

Appendix: 3

Google scholar search strategy: 591

Appendix 3 Questionnaire- Operational Challenges B/W Self Inflating bag (SIB) and Automated Resuscitation device (ARD)

QUESTIONAIRE	**OPERATIONAL CHALLENGES B/W SELF INFLATING BAG (SIB) AND AUTOMATED RESUSCITATION DEVICE (ARD) DEVICES FOR NEONATAL RESUSCITATION**	
DATE:	HOSPITAL:	REPORT TAKEN BY:

S.No	Description	Self-Inflating Ambu Bag (SIB)	T-Piece Resuscitator (ARD)
1	Which device is used in your NICU		
2	Since how long you have been using this device *(Less than 1 yr, 1-5 yrs, More than 5yrs)*		
3	How often is the device used. *(weekly, monthly, once in 6 months, once in a yr, never)*		
4	How did you learn to use this device? *(Medical or Nursing College/ Practical hands-on)*		
	Staff Related		
5	How many No. of staff are required for assistance when you use this device		
6	Who operates the device primarily (*Doctor, Nurse, Technician, etc.)*		
	Device Usage Characteristics		
7	Is the device User-friendly? *(Yes/No)*		
8	If Point 7 is No, then please describe why?		
9	Time taken to initiate treatment with the device *(0-2 min, 2-5, >5 min)*		
10	Do you consider the device safe to use *(Yes/No)*		
	Maintenance Related		
11	How easy is it to maintain the equipment on regular basis (*Very Difficult, Difficult, Easy, Very Easy)*		
12	How often does the device breakdown *(very often, rarely, never)*		
13	How much time is taken to get a device repaired. *(<1 day, 1 week, >week, cannot be repaired)*		
14	Accessibility of spare parts *(Easy, Difficult, Don't know)*		
15	Are there standby devices in case of breakdown *(Yes/No)*		
16	Is there a regular protocol for device maintenance *(Yes/No)*		
17	Is there a defined time period for device inspection *(Yes/No)*		
	Adverse Events		
18	Did you observe any device related adverse events (Intubation/Mortality) *(0, 1-10, >10)*		
19	What was the adverse event?		

Appendix 4: State-wise Neo-natal Mortality Rate during 2016 [56]

Sl.No	State	2016 - Total	2016 - Rural	2016 - Urban
India	India	24	27	14
1	Andhra Pradesh	23	27	11
2	Assam	23	24	13
3	Bihar	27	28	17
4	Chhattisgarh	26	27	20
5	Delhi	12	16	12
6	Gujarat	21	27	13
7	Haryana	22	24	16
8	Himachal Pradesh	16	16	15
9	Jammu and Kashmir	18	19	15
10	Jharkhand	21	23	13
11	Karnataka	18	22	10
12	Kerala	6	7	4
13	Madhya Pradesh	32	35	20
14	Maharashtra	13	17	9
15	Odisha	32	33	24
16	Punjab	13	13	12
17	Rajasthan	28	31	17
18	Tamil Nadu	12	16	9
19	Telangana	21	25	15
20	Uttar Pradesh	30	32	19
21	Uttarakhand	30	32	24
22	West Bengal	17	17	14

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67