Resource Center Health Technology Assessment, AIIMS Jodhpur

Outcome Report for Inj. Gentamicin in neonatal sepsis by ANMs before referral

Principle Investigator: **Dr Kuldeep Singh**
Dean Academics, AIIMS Jodhpur

Co-investigators: **Dr Vibha Joshi**
Health Economist, Resource Centre HTA, AIIMS Jodhpur

Dr Pankaj Bhardwaj
Additional Professor
Community Medicine and Family Medicine
Coordinator School of Public Health AIIMS Jodhpur

Dr Neeraj Gupta
Additional Professor, Department of Neonatology
AIIMS Jodhpur

Dr Nitin Joshi
School of Public Health AIIMS Jodhpur

Dr Oshima Sachin
Scientist-D, HTAIn Secretariat
Department of Health Research
Ministry of Health and Family Welfare

Introduction

Sepsis is the commonest cause of neonatal mortality; it is responsible for about 30-50% of the total neonatal deaths in developing countries. (1)(2) India has the greatest incidence of clinical sepsis (17,000/ 1,00,000 live births) among the three million yearly neonatal sepsis cases (2202/ 1,00,000 live births) globally. (3) It is estimated that up to 20% of neonates develop sepsis and approximately 1% die of sepsis-related complications. (2) Neonatal mortality related to sepsis can be prevented with the prevention of sepsis itself. This includes timely recognition, rational antimicrobial therapy, and aggressive supportive care. The incidence of neonatal sepsis according to the data from National Neonatal Perinatal Database (NNPD, 2002-03) is 30 per 1000 live births. (4) In India sepsis is found to be one of the commonest causes of neonatal mortality contributing to 19% of all neonatal deaths. (5)

Treatment must be effective against the causative pathogen and safe for the newborn. World Health Organization's pocketbook of Hospital Care for Children, currently recommends treatment with parenteral ampicillin (or penicillin) and gentamicin in young infants for 10-14 days. (6)

Under the current health system, ANMs are the key frontline health workers who interact directly with the community and are responsible for the delivery of the Reproductive and Child Health Programme. Based on the WHO recommendations, NHM, and MoHFW has formed an Operational guideline on the use of Gentamicin by ANMs for the management of sepsis in young infants under specific situations in February 2014. According to this operational guideline, ANMs are skilled in administering injections and in injection safety practices. They have been regularly giving injectable vaccines to infants and emergency injectable medications (intramuscular injection magnesium sulphate, injection oxytocin, intravenous fluids, etc.) to mothers. Moreover, they have been trained under the IMNCI programme to detect young infants with Possible Serious Bacterial Infection (PSBI) or suspected sepsis. (7)(8)

In many parts of the country, young infants are not able to access healthcare facilities on time to seek treatment. Hence under the circumstances where referral is not possible or is refused, ANMs are best placed to be trained to administer appropriate antibiotic treatment to young infants for management of cases of suspected sepsis in a newborn where referral is not feasible or refused; pre-referral or for the completion antibiotic treatment. (7) But there is a paucity of the literature, that assess the ground-level scenario of this strategy and its implication.

The objective of this study is to assess the cost implications of delivery of Gentamicin by ANM to manage neonatal sepsis and assess the incremental cost-effectiveness ratio in terms of cost per neonatal death averted or cost per QALY gained.

Methods:

Study Setting-

A Health Technology Assessment antibiotic therapy by ANM to manage neonatal sepsis in the Indian context

Perspective-

A Health system, as well as an abridged societal perspective, was employed(costs due to productivity losses were not to be taken into account) as per the HTAIn reference case.

Intervention and Comparator –

A Decision tree model was constructed for comparing three scenarios in the context of management of neonatal sepsis. Scenario 1 describes a pre-referral dose of Inj. Gentamicin by ANM along with oral amoxicillin and treatment in the health facility for the neonate with signs of sepsis**,** scenario 2 is a pre-referral dose of Inj. Gentamicin along with oral amoxicillin by ANM and treatment at home when a referral is refused and scenario 3 is a current scenario where ANM refers neonates with sepsis to a health facility without a pre-referral dose of Inj. Gentamicin.

Input model parameters-

Parameters pertaining to the study were derived from published literature through systematic searches /targeted reviews. In India, the Infant mortality rate per 1000 live births is 32 and the neonatal mortality rate per 1000 live birth in India is 23. (9)

Complications related to neonatal sepsis occur as short-term and long-term complications. Long-term complications include bronchopulmonary dysplasia, cerebral palsy, retinopathy of prematurity, neurodevelopmental delay, visual or auditory impairment, long-term growth impairment, atopic diseases, and chronic lung disease in childhood. The rate of complications varied from 3.5% to 53.6%, so, the median was 28. 6%, of the rates, were taken as a base case value for the rate of recovery with disability. (10)

The efficacy of WHO's recommended treatment for infant sepsis with Gentamicin is reported in the literature. (6) The feasibility and efficacy of gentamicin for treating neonatal sepsis were derived from a systematic review conducted by Jaiswal et al.(11) Data for the case fatality rate (in the first/second week or the first month of life), need for referral to a higher center were derived from Band et al (1999) (1) and Awasthi et al(2020) (12)

Feasibility, accessibility, and availability of ANM-

ANMs have been trained under the IMNCI programme to detect young infants with Possible Serious Bacterial Infection (PSBI) or suspected sepsis. Their availability is reported in the guidelines.

According to operational guidelines, ANMs are skilled in administering injections and in injection safety practices. They have been regularly giving injectable vaccines to young infants and emergency injectable medications. On consultation exercises, it was found that ANMs show resistance to injecting Gentamicin administered to neonates as side effects of this drug may even lead to the death of neonates. In contrast, a study in Nepal reported that when Gentamicin was used in the uniject prefilled injection system, it is a feasible and acceptable option for the treatment of possible neonatal sepsis in the community. (13)

Estimation of cost

Cost of the intervention strategy, of giving pre-referral dose by ANM to neonates with features of sepsis, included direct and indirect costs. Direct costs comprise of training cost of ANM, cost of service delivery of the intervention, cost of Hospital stay(in a PHC/CHC) (Prinja et al 2016) (14), and travel/referral cost (Prinja et al 2013,2014) (15)(16) were taken from the respective studies reported in the literature and the cost data was adjusted to the current year. The current market price of the cost of the consumable drugs was considered and the cost of treating the most common complication (eg: cerebral palsy or Mental retardation) in a tertiary centre was taken from the Costing of health Services of India (CHSI) initiative of DHR/Costing database of PGIMER. A primary cost data collection was conducted where cost data was not available within the CHSI database. The indirect cost which comprises time cost in terms of loss of wages and time spent was not considered in the study.

Health-Related Quality of Life

Health outcomes were given in the form of neonatal death averted and QALY gained due to the use of the intervention (of giving pre-referral dose by ANM to neonates with features of sepsis)in neonates.(17)(18)(19)

Studies reporting HRQoL in infants with neonatal sepsis features with and without antibiotic treatment as well as in infants who have recovered from neonatal sepsis with disability were collected from literature and used for the decision tree**.**

Table No. 1

Transition Probabilities	Values	Cases
Neonate with A pre-referral and Treatment in Health Facility		
Probability of Death after administering Pre-referral dose (Genta+Amox) to an neonate by ANM and treatment at health facility	0.0280	6
Probability of Recovery after administering Pre-referral dose (Genta+Amox) to an neonate by ANM and treatment at health facility	0.6860	137
Probability of Recovery with Disability after administering Pre-referral dose (Genta+Amox) to an neonate by ANM and treatment at health facility	0.2860	57
Neonate with Preferral and treatment at home by ANM		
Probability of Death after administering Pre-referral dose (Genta+Amox) to an neonate by ANM and treatment at home	0.0690	55
Probability of Recovery after administering Pre-referral dose (Genta+Amox) to an neonate by ANM and treatment at home	0.6450	516
Probability of Recovery with after administering Pre-referral dose (Genta+Amox) to an neonate by ANM and treatment at home	0.2860	229
Neonate with No Preferral and treatment at health Facility		
Probability of Death of neonate with sepsis without Pre-referral dose (Genta+Amox) by ANM and treatment at health facility	0.1430	25
Probability of Recovery of neonate with sepsis without Pre-referral dose (Genta+Amox) by ANM and treatment at health facility	0.5710	100
Probability of Recovery with Disability of neonate with sepsis without Pre-referral dose (Genta+Amox) by ANM and treatment at health facility	0.2860	50

Table No. 2

Cost Parameters	Value	Curr. Val(Inf)	Total	Tot Val(Inf)
Cost of Gentamicin	2.5	4	12.5	20
Cost of Amoxicillin	5	10	50	100
General Admininstration	22	44	22	44
Program Cost (ANM Training)	57	115	57	115
Per Neonate OPD Cost of First Referral	274	554	274	554
Per Neonate IPD Cost of District Hospital	3854	7787	3854	7787
Per Neonate OOP For IPD	1900	3839	1900	3839
Post-Natal Cost	751.4	1517	751.4	1517
Cost of treatment at SNCU	4581	9256		9256

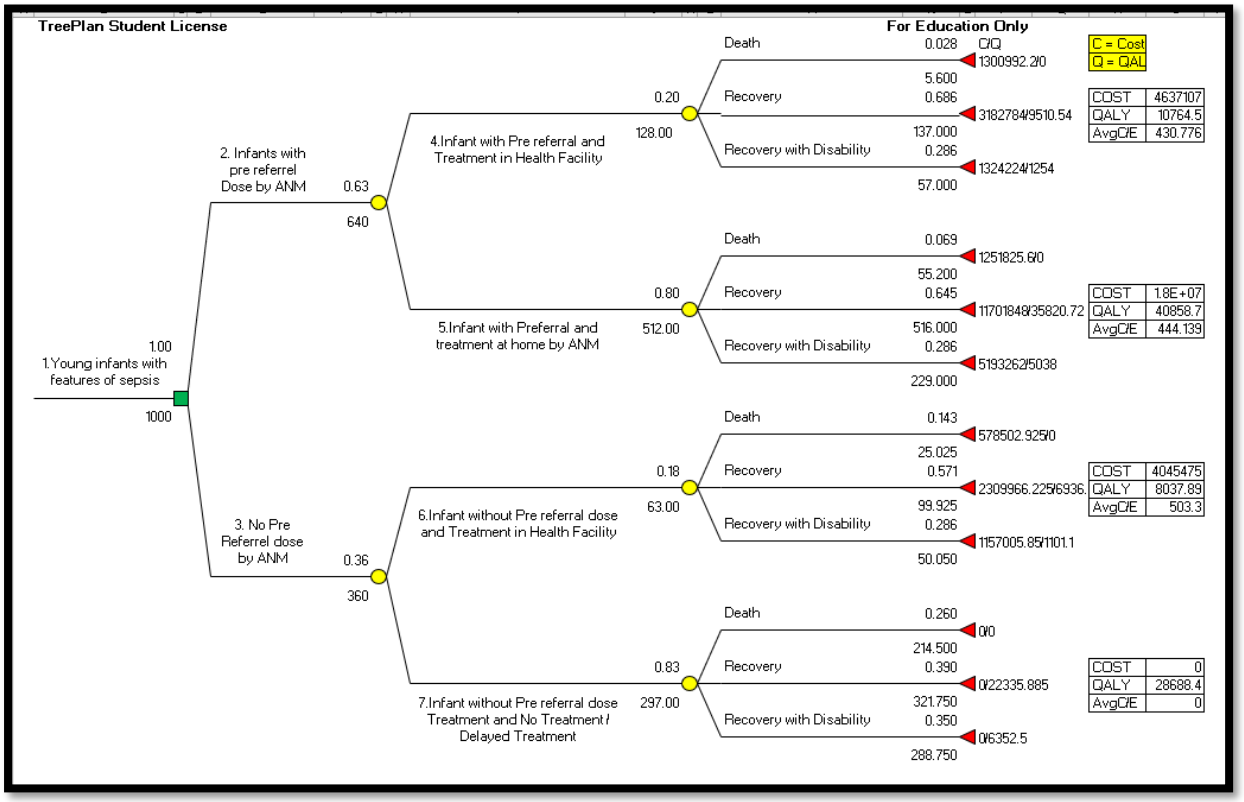
Table No. 3

Quality of life	Value
Death	0.00
Recovery	1.00
Recovery with Disability	0.40
Life Expectancy	**Value**
Death	0.00
Recovery	69.42
Recovery with Disability	55.00

Results:

A Decision tree model for estimating the incremental cost-effectiveness ratio in terms of the cost per QALY gained is illustrated in fig.1. The model describes three scenarios. Scenario 1 describes, a pre-referral dose of Gentamicin by ANM and treatment in the health facility for an neonate with signs of sepsis, scenario 2 is a pre-referral dose of Gentamicin by ANM and treatment at home when a referral is refused and scenario 3 is the current scenario where no pre-referral dose of Gentamicin is given by ANM to the neonate with sign os sepsis and treatment in the health facility.

Fig.1



Estimation of cost and QALY and average cost-effectiveness ratio for each scenario is shown in table no.4

The total cost estimated for an neonate with the sign of sepsis given a pre-referral dose of Gentamicin by ANM and treatment at home when a referral is refused (scenario 2) was higher than an neonate with the sign of sepsis given a pre-referral dose of Gentamicin by ANM and treatment in a health facility (scenario 1) and neonate with the sign of sepsis but no pre-referral dose of Gentamicin is given by ANM and treatment in a health facility(scenario 3).

An neonate with the sign of sepsis given a pre-referral dose of Gentamicin by ANM and treatment at home when a referral is refused (scenario 2) had a higher total QALY than neonate with the sign of sepsis given a pre-referral dose of Gentamicin by ANM and treatment in a health facility (scenario 1) and lowest in neonate with the sign of sepsis but no a pre-referral dose of Gentamicin by ANM and treatment in a health facility (scenario 3).

ICER of scenario 1(pre-referral dose of gentamicin) versus scenario 3 (no-pre-referral dose and treatment at health facility) was calculated to be Rs.216.98 cost per QALY gained. While ICER of Implementing scenario 1(Pre-Referral Dose of Gentamicin) versus scenario 2 (Pre-Referral Dose and Treatment at Home by ANM) was Rs. 448.91 cost per QALY gained and the highest cost per QALY gained was calculated for scenario 2 (Pre-Referral Dose of Gentamicin and

Treatment at Home by ANM versus scenario 3 (No-Pre-Referral Dose and Treatment at Health Facility).

The ICER for scenario 1 versus scenario 3 is far lower than WTP threshold of one times India's GDP per capita at INR 137,945, hence administering a pre-referral dose of gentamicin along with oral amoxicillin by ANM

Table No. 4

Neonate with A pre-referral and Treatment in Health Facility						
	COST/neonate	**Death**	**Recovery**	**Recovery with Disability**	**Total**	**Average cost-effectiveness ratio (Cost/QALY)**
Cases		**5.60**	**137.00**	**57.00**	**128**	
Cost	**23,232**	**130099.2**	**3182784**	**1324224**	**46,37,107.2**	
QALYs		**0**	**9510.54**	**1254**	**10764.54**	**430.7761595**
Neonate with A pre-referral and Treatment at Home						
	COST/neonate	**Death**	**Recovery**	**Recovery with Disability**	**Total**	
Cases		**55.20**	**516.00**	**229.00**	**512**	
Cost	**22678**	**1251825.6**	**11701848**	**5193262**	**1,81,46,935.6**	
QALYs		**0**	**35820.72**	**5038**	**40858.72**	**444.1386221**
Neonate with No A pre-referral and Treatment in Health Facility						
	COST/neonate	**Death**	**Recovery**	**Recovery with Disability**	**Total**	
Cases		**25.03**	**99.93**	**50.05**	**63**	
Cost	**23,117**	**578502.925**	**2309966.225**	**1157005.85**	**40,45,475**	
QALYs		**0**	**6936.7935**	**1101.1**	**8037.8935**	**503.3003983**

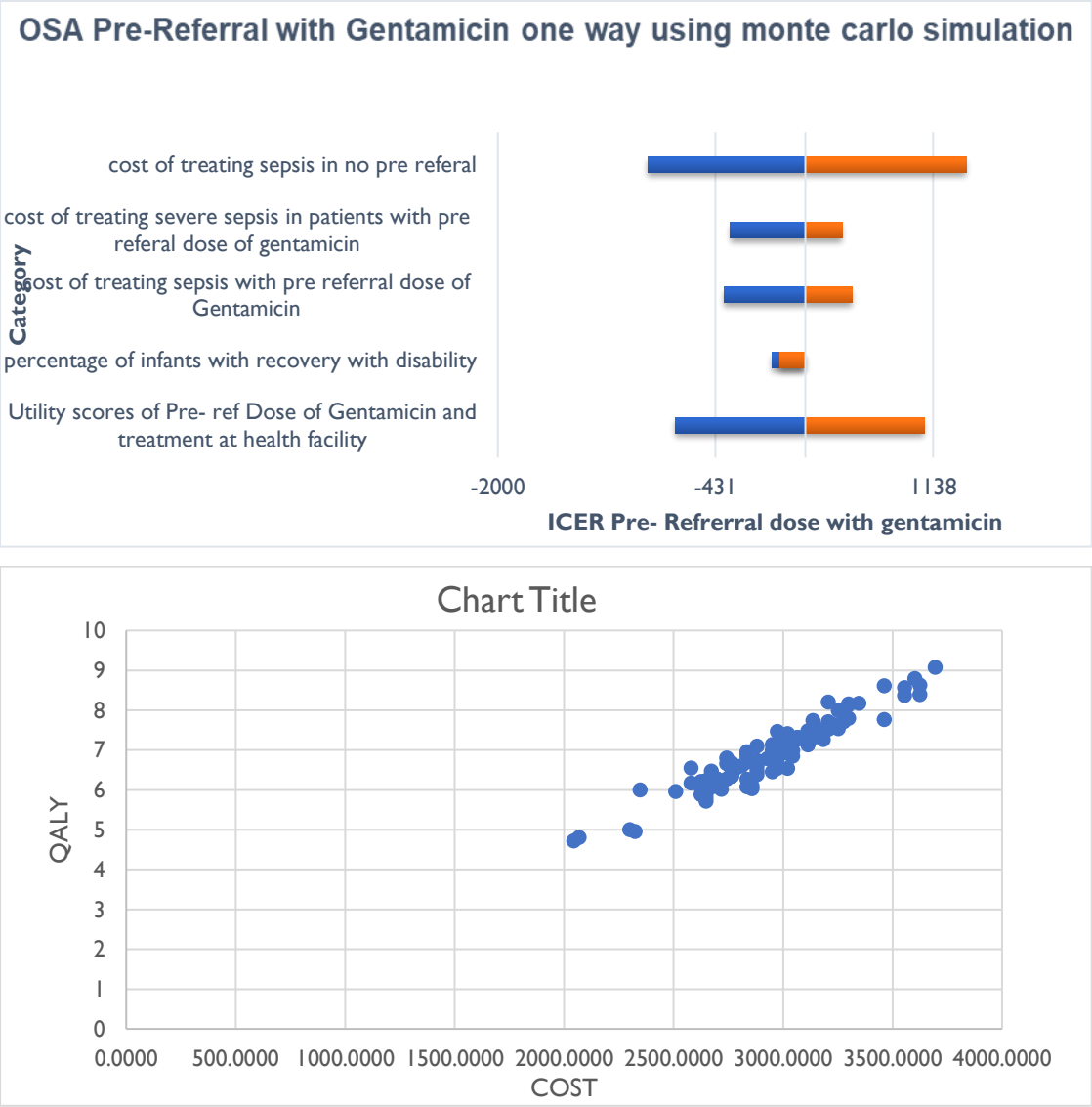
Sensitivity Analysis

A Tornado diagram based on one-way sensitivity analysis is presented in fig 2. It shows the four input parameters that affect the ICER the most. For all changes in input parameters, a pre-referral dose of Gentamicin by ANM and treatment in a health facility for an neonate with signs of sepsis remains cost-effective

Fig 3 shows incremental QALYs on the Y-axis and incremental cost on the X-axis. The 100 ICER points from the one-way sensitivity analysis results from scenario1 versus scenario 3 are

depicted as blue dots. 100% of ICER values from Monte Carlo simulations were cost-effective and fell in the upper right quadrant of the cost-effectiveness plane. Hence, implementing the provision of administering a pre-referral dose of gentamicin along with oral amoxicillin by ANM in the public health system of India would prove to be cost-effective.

Fig 2



To the best of our knowledge, this is the first study in India to provide insights on providing a pre-referral dose of Gentamicin by ANMs in neonates with the sign of sepsis. This study demonstrated that implementing the Operational Guidelines of the Government of India for use of Gentamicin by ANMs for management of sepsis in young neonates which states that ANMs should administer Injection Gentamicin along with oral Amoxicillin to young neonates [0 – 2 months] suspected with sepsis will prove to be cost-effective public health program.

References

1. Bang AT, Bang RA, Baitule SB, Reddy MH, Deshmukh MD. Lancet Field Trial. 2005;354:1–7.
2. Stoll BJ. The global impact of neonatal infection. Clin Perinatol [Internet]. 1997;24(1):1–21. Available from: http://dx.doi.org/10.1016/S0095-5108(18)30181-7
3. Fleischmann-Struzek C, Goldfarb DM, Schlattmann P, Schlapbach LJ, Reinhart K, Kissoon N. The global burden of paediatric and neonatal sepsis: a systematic review. Lancet Respir Med [Internet]. 2018;6(3):223–30. Available from: http://dx.doi.org/10.1016/S2213-2600(18)30063-8
4. M S, VK P, ON B. National Neonatal-Perinatal Database 2002-2003. NNPD Nodal Cent Dep Pediatr WHO Collab Cent Newborn Train Res All India Inst Med Sci [Internet]. 2005;63–6. Available from: http://www.newbornwhocc.org/pdf/nnpd_report_2002-03.PDF
5. UNICEF. Newborn and child health. Unicef India. 2017;1–7.
6. Downie L, Armiento R, Subhi R, Kelly J, Clifford V, Duke T. Community-acquired neonatal and infant sepsis in developing countries: Efficacy of WHO's currently recommended antibiotics - Systematic review and meta-analysis. Arch Dis Child. 2013;98(2):146–54.
7. Welfare F. Operational Guidelines Use of Gentamicin by ANMs for management of sepsis in young infants under specific situations Ministry of Health and Family Welfare Government of India. 2014;
8. WHO Guidelines. Managing possible serious bacterial infection in young infants when referral is not feasible nrhmmanipur.org. 2011. Skills That Save Lives. [Internet]. 2105 [cited 2022 May 25]. Available from: https://nrhmmanipur.org/wp-content/uploads/2011/01/ASHA-Module-7.pdf
9. Census of India. Sample Registration System Statistical Report 2011. Off Regist Gen Census Com India Minist Home Aff Gov India [Internet]. 2011;11–28. Available from: http://www.censusindia.gov.in/vital_statistics/SRS_Report/9Chap 2 - 2011.pdf
10. Bakhuizen SE, De Haan TR, Teune MJ, Van Wassenaer-Leemhuis AG, Van Der Heyden JL, Van Der Ham DP, et al. Meta-analysis shows that infants who have suffered neonatal sepsis face an increased risk of mortality and severe complications. Acta Paediatr Int J Paediatr. 2014;103(12):1211–8.
11. Jaiswal N, Singh M, Kondel R, Kaur N, Thumburu KK, Kumar A, et al. Feasibility and efficacy of gentamicin for treating neonatal sepsis in community-based settings: a

systematic review. World J Pediatr. 2016;12(4):408–14.

12. Awasthi S, Kesarwani N, Verma RK, Agarwal GG, Tewari LS, Mishra RK, et al. Identification and management of young infants with possible serious bacterial infection where referral was not feasible in rural Lucknow district of Uttar Pradesh, India: An implementation research. PLoS One [Internet]. 2020;15(6):1–20. Available from: http://dx.doi.org/10.1371/journal.pone.0234212
13. Coffey PS, Sharma J, Gargi KC, Neupane D, Dawson P, Pradhan Y V. Feasibility and acceptability of gentamicin in the Uniject prefilled injection system for community-based treatment of possible neonatal sepsis: The experience of female community health volunteers in Nepal. J Perinatol. 2012;32(12):959–65.
14. Prinja S, Gupta A, Verma R, Bahuguna P, Kumar D, Kaur M, et al. Cost of delivering health care services in public sector primary and community health centres in north India. PLoS One. 2016;11(8):1–15.
15. Prinja S, Bahuguna P, Lakshmi PVM, Mokashi T, Aggarwal AK, Kaur M, et al. Evaluation of publicly financed and privately delivered model of emergency referral services for maternal and child health care in India. PLoS One. 2014;9(10):1–11.
16. Prinja S, Manchanda N, Aggarwal AK, Kaur M, Jeet G, Kumar R. Cost & efficiency evaluation of a publicly financed & publicly delivered referral transport service model in three districts of Haryana State, India. Indian J Med Res. 2013;138(DEC):1003–11.
17. Einerson BD, Grobman WA, Miller ES. Cost-effectiveness of risk-based screening for cervical length to prevent preterm birth. Am J Obstet Gynecol [Internet]. 2016;215(1):100.e1-100.e7. Available from: http://dx.doi.org/10.1016/j.ajog.2016.01.192
18. Whitehead SJ, Ali S. Health outcomes in economic evaluation: The QALY and utilities. Br Med Bull. 2010;96(1):5–21.
19. Pharoah POD, Stevenson RC, Cooke RWI, Sandu B. Costs and benefits of neonatal intensive care. Arch Dis Child. 1988;63(7 SPEC NO.):715–8.