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Cost-effectiveness analysis of implementing an integrated neonatal care kit to reduce neonatal infection in rural Pakistan

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ABSTRACT

Objective To evaluate the cost-effectiveness of distribution of the integrated neonatal care kit (iNCK) by community health workers from the healthcare payer perspective in Rahimyar Khan, Pakistan.

Setting Rahimyar Khan, Pakistan.

Participants N/A.

Intervention Cost-utility analysis using a Markov model based on cluster randomised controlled trial (cRCT: NCT 02130856) data and a literature review. We compared distribution of the iNCK to pregnant mothers to local standard of care and followed infants over a lifetime horizon.

Primary and secondary outcome measures The primary outcome was incremental net monetary benefit (INMB, at a cost-effectiveness threshold of US$15.50), discounted at 3%. Secondary outcomes were life years, disability-adjusted life years (DALYs) and costs.

Results At a cost-effectiveness threshold of US$15.50, distribution of the iNCK resulted in lower expected DALYs (28.7 vs 29.6 years) at lower expected cost (US$52.50 vs 55.20), translating to an INMB of US$10.22 per iNCK distributed. These results were sensitive to the baseline risk of infection, cost of the iNCK and the estimated effect of the iNCK on the relative risk of infection. At relative risks of infection below 0.79 and iNCK costs below US$25.90, the iNCK remained cost-effective compared with current local standard of care.

Conclusion The distribution of the iNCK dominated the current local standard of care (ie, the iNCK is less costly and more effective than current care standards). Most of the cost-effectiveness of the iNCK was attributable to a reduction in neonatal infection.

Strengths and limitations of this study

► This study is the first cost-effectiveness analysis using empiric randomised controlled trial data to evaluate a bundle of newborn interventions (integrated neonatal care kit, iNCK) in comparison to local standard of care.

► This cost-effectiveness analysis would be improved by additional empiric data describing the effect of iNCK use on maternal mortality and the detection and management of neonatal hypothermia.

► Further study is needed to evaluate the association between iNCK compliance (eg, correct use of individual kit components) and risk of neonatal infection and other key health outcomes including mortality.

INTRODUCTION

Neonatal mortality is the primary contributor to death among children under 5, with one-third of these deaths attributable to infection.[1] With 46 neonatal deaths per 1000 live births, Pakistan has the highest neonatal mortality rate (NMR) in the world.[1] Randomised controlled trials (RCTs) and pooled analyses in other countries have demonstrated the efficacy of several strategies to reduce neonatal mortality including: use of a clean birth kit (CBK) (OR: 0.52, 95% CI: 0.39 to 0.68),[2] use of chlorhexidine for cord cleansing (relative risk (RR): 0.77, 95% CI: 0.63 to 0.94),[3] oil-based skin emollient application to prevent hypothermia and preserve the skin barrier reducing infection (RR: 0.73, 95% CI: 0.56 to 0.94)[4] and community interventions to improve clean birth practices to reduce NMRs (RR: 0.52, 95% CI: 0.39 to 0.68).[2] Despite evidence to support several clean birth care practices, their use in Pakistan is variable. In a recent survey of 225 mothers following delivery in Sindh province, only 32% of those who delivered at home reported use of a clean delivery kit (new blade, sterilised disposable gloves, soap, gauze, cotton balls, antiseptic solution, umbilical cord clamp and polythene sheet), 24% of women reported use of cord antiseptics and 45% reported cutting the cord with a sterile blade.[5] Other reported practices include application of skin emollients (ghee, mustard oil and lotion) and substances applied to the cord (turmeric, ghee, surma and oil).[6] Individual financial constraints, difficulty

accessing CBKs, antiseptic solution and emollients and cultural beliefs hinder the widespread uptake of these potentially life-saving interventions.[7]

While the efficacy of individual interventions has been demonstrated, the effectiveness of combined interventions remains unclear. In addition, the effectiveness of combined kit components, implemented in community-based settings and delivered entirely by community health workers, remained largely unstudied. Recently, a cluster RCT (cRCT: NCT 02130856) was conducted in rural Pakistan to evaluate the effect of distribution of an integrated neonatal care kit (iNCK) by community Lady Health Workers (LHWs) on neonatal health outcomes.[6 8] LHWs are government-funded, trained community healthcare providers who are each responsible for family planning and primary healthcare services for 150–200 homes. LHWs provide basic reproductive, maternal, newborn and child health education, basic curative care and are trained to identify neonatal danger signs and recommend referral.[6] While LHWs do not attend births directly, promotion of clean birth practices, use of skilled birth attendants and timely referral to emergency obstetric or neonatal care are an integral part of their role in Pakistan.[9] The iNCK contained a CBK (gloves, soap, clean plastic sheet, sterile blade and cord clamps), 4% chlorhexidine solution, sunflower oil emollient, a continuous temperature monitor sticker, a blanket and an instant heat pack. In addition, during the cRCT, a weighing scale was distributed to LHWs to enable them to screen newborn infants for low birth weight.[6] Neonatal mortality was not significantly different between treatment groups (risk ratio: 0.83, 95% CI: 0.58 to 1.18; p=0.30). However, the risk of omphalitis, irrespective of severity, was 32% lower in the intervention arm compared with the control arm (RR: 0.68, 95% CI: 0.48 to 0.98; p=0.04).[6]

We aimed to assess the cost-effectiveness of distribution of an iNCK by LHWs to pregnant mothers compared with local standard of care in rural Pakistan from a governmental healthcare payer perspective. Distribution of an iNCK by LHWs, financed by the government healthcare payer, may contribute to circumventing barriers to uptake of clean birth practices.

METHODS

We conducted a model-based cost-effectiveness analysis of iNCK distribution by LHWs compared with the current standard of care in rural Pakistan from the perspective of the governmental healthcare payer. The governmental payer perspective was used to inform whether the cost of widespread iNCK distribution financed by the government would be cost-effective due to improved neonatal outcomes and associated decreased healthcare utilisation costs to the government payer.

Trial design, eligibility criteria and study procedures for the LHWs and the family members have been fully described previously.[6 10] In brief, all women in the third trimester of pregnancy within participating randomised

clusters were considered eligible if they intended to stay in the study catchment area for at least 1 month after delivery. Participating LHWs identified pregnant women and notified the study team. A data collector visited pregnant women, explained the study and obtained written informed consent. The LHW delivered the iNCK and/or the standard of care. All participants had agency to opt out of the study at any time and for any reason.

Standard of care, included community-based antenatal and postnatal care by LHWs and may or may not have included the use of other clean birth practices. Standard antenatal care by LHWs (in both groups of the cRCT) includes delivery of basic reproductive, maternal, newborn and child health education, promotion of healthy behaviour, basic curative care and identification of neonatal danger signs and referrals as appropriate.[6] Several alternative clean birth and newborn interventions were used in the cRCT comparator group, which were summarised in the model as use of any CBK and/or a cord antiseptic (Dettol). In the cRCT comparator arm, 50.3% used any CBK and 60.7% used a cord antiseptic.[6]

For the purposes of the iNCK intervention, LHWs were additionally instructed on the use of the kit, the weighing scale, application of chlorhexidine to the umbilicus, education of sunflower oil emollient massage for the newborn and use of the thermal pack. At the time of delivery, LHWs taught mothers how to use each iNCK component and, if present, other caregivers were engaged in the teaching session. Pregnant women were taught to apply chlorhexidine to the umbilical stump once daily from day 1 to day 10, and to apply one ThermoSpot sticker to the skin over the carotid artery on day 1 and leave it in place until day 14. Women were taught the meaning of each sticker colour and the actions to be taken if ThermoSpot indicated fever, cold stress or hypothermia. Sunflower oil was to be massaged over the newborn's body once daily starting from day 3 until day 28.

Costs associated with the iNCK, hospitalisation or outpatient treatment for infection and the treatment for long-term sequelae were included. Given that significant sequelae from neonatal sepsis can have lifelong effects, a lifetime time horizon was selected. A 3% discount rate was applied to life years, DALYs and costs, as recommended by the WHO.[11]

The cost-effectiveness threshold (CET) was set at US$15.50 per DALY, corresponding to 1% of Pakistan's GDP per capita in 2019, a conservative estimate of health spending.[12] Though the WHO recommends a CET equivalent to a country's GDP per capita, this is perceived as controversial for low-income and middle-income countries (LMICs).[8 13 14] Published estimates of CETs range from 1% to 59% GDP per capita in LMICs due to low healthcare spending.[8 13 14]

Primary outcomes were disability-adjusted life years (DALYs), total costs and incremental net monetary benefit (INMB; CET of US$15.50).[8] DALYs were selected as a standardised measure of cost-effectiveness as recommended by the WHO, National Institute of Health and
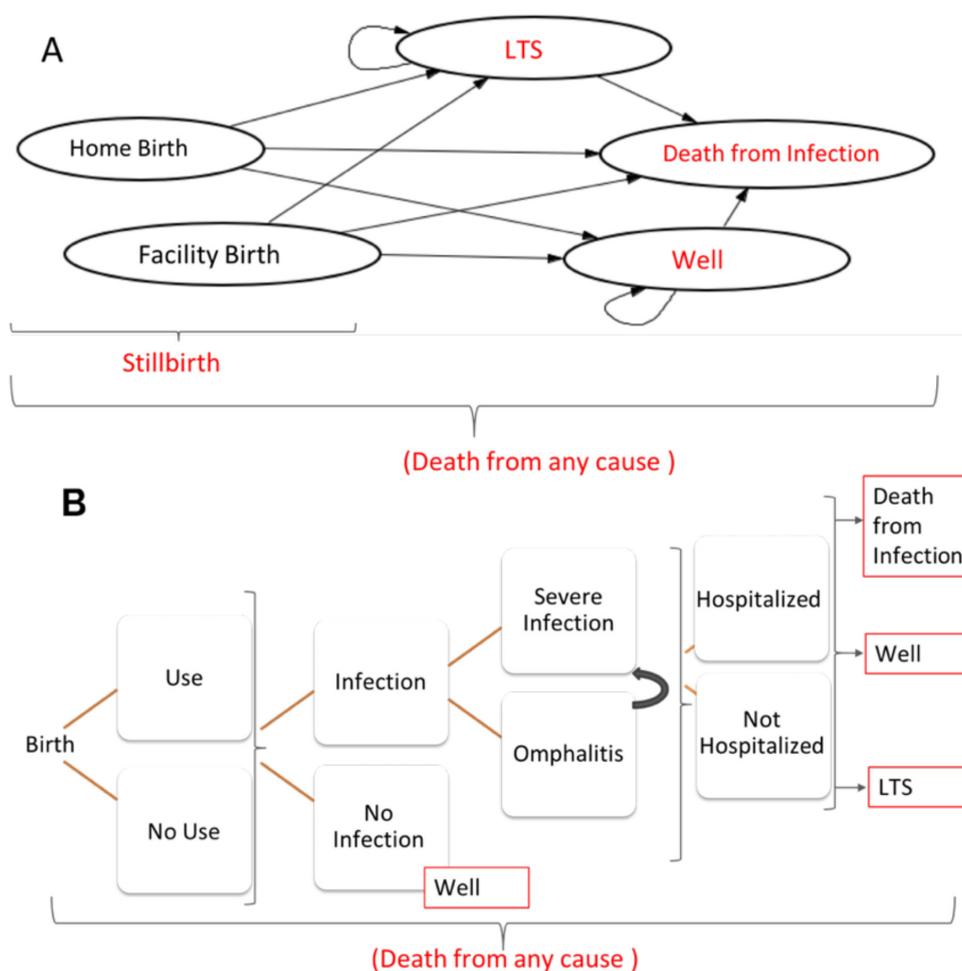
Figure 1 Model schematic diagram. (A) Markov Health State Transition Diagram. A child can be born at home or facility and then proceed to either the states of long-term sequelae (LTS), well or death. Stillbirth infants are accounted for in the death absorbing state. (B) Tree diagram after birth. At birth, a child can either be in the cohort to which an iNCK was distributed or not. In the intervention arm, the elements of the iNCK may be used or not. Similarly, in the control arm, other clean birth and newborn care strategies may or may not be used. The neonate may develop an infection which could either be severe infection or omphalitis (mild/moderate cord infection). If they develop a cord infection, they may go on to develop a severe infection. In the presence of infection, they may be hospitalised or receive outpatient care and proceed to either the death, well or LTS states. If they have no infection, they proceed to the well state. At any point, they can die from unrelated causes. iNCK, integrated neonatal care kit.

Bill and Melinda Gates Foundation. Secondary outcome was life years.

Model structure

A Markov cohort model was developed (figure 1) using TreeAgePro 2018 software (V.2020 r 1.2, Grey Matter, England). Health outcomes and cost were modelled over a lifetime time horizon in 1-year time steps (ie, cycle length in a Markov model) to encapsulate the neonatal infections and sequelae occurring in the first 28 days of life, the risk of all-cause mortality within 1 year of age and thereafter to model the impact of sequelae over the lifetime time horizon. The initial health states were either birth at home or facility, accounting for stillbirths. Liveborn neonates were followed over time for development of a neonatal infection, categorised as omphalitis (cord infection) or severe infection. It was assumed that

infants who had both cord infection and severe infection developed the cord infection first followed by secondary severe infection. Causes of neonatal infection other than omphalitis (eg, pneumonia, sepsis) were grouped under severe infection. Neonatal infection was assumed to have occurred only once. It was also assumed that all children with severe infection who did not receive hospital care received outpatient therapy. At the end of the first year, all live born infants have lived 1 year and transitioned to one of three health states: well, death due to infection, survival with severe neurodevelopmental or learning impairment, with or without CP. The probability of all-cause mortality at 1 year was accounted for.

Model data

Data to inform the model were primarily drawn from the iNCK cRCT in which clusters were randomised to

receive either the iNCK or local standard of care. This was supplemented by a comprehensive literature review, local data sources and expert opinion. All variables and their supporting references are summarised in table 1. The cRCT data provided probabilities for location of delivery (home vs facility), reported use of a CBK and/or cord antiseptic (presumed iNCK CBK in the intervention arm or other CBK with or without Dettol cord antiseptic in the control arm), baseline risk of any infection or omphalitis and RR of severe infection stratified by delivery location and reported use of a CBK and/or cord antiseptic (presumed iNCK in the intervention arm or other CBK with or without Dettol cord antiseptic in the control arm). Severe infection was a priori defined in the cRCT as the presence of any of: seizures, fast respiratory rate (60 breaths/min or more), fever, severe chest in drawing, poor feeding and abnormal activity.[15] In a post-hoc sensitivity analysis, poor feeding and/or abnormal activity, which were reported at higher than anticipated rates, were removed from the initial definition of severe infection. In the cost-effectiveness model, the revised post-hoc definition of severe infection was applied to use a more specific case definition and exclude symptoms that may represent other causes of illness than infection. The probability of severe infection using the revised definition was not stratified according to whether mothers reported use of a CBK.

We assumed that published data from studies conducted in Pakistan were representative of our study population. Variables drawn from the literature included probability of hospitalisation given severe infection, probability of death due to severe infection given treatment in hospital, probability of severe neurodevelopmental impairment (NDI, with or without CP) following severe infection and annual probability of death. The probabilities of sequelae of neonatal severe infection were drawn from an international meta-analysis of studies in LMICs evaluating neonatal outcomes after sepsis among hospitalised low birth weight infants.[16] The annual mortality rate (AMR) for severe mental retardation in Pakistan was used as a proxy for AMR among patients with severe NDI given that data specific to NDI were not available.[17] Data for three variables (probability of hospitalisation if mild/moderate omphalitis, probability of mild/moderate omphalitis to severe and RR of death due to severe infection if not hospitalised) could not be obtained from the literature or cRCT data, thus were based on paediatric infectious diseases and paediatric critical care expert opinions (Morris and Muttalib, personal communication, 2018). The effect of compliance of appropriate use of the iNCK on risk of infection was not modelled.

Health-related utilities (DALYs) were designated for the death state (disability weight (DW) of 1), the long-term sequelae state (DW for CP) and the well state (DW of 0). There is no published DW for mild/moderate omphalitis in neonates, thus a weighted average of the total proportion of mild omphalitis and moderate omphalitis was multiplied by the respective DWs for acute mild

infection and acute moderate infection from the Global Burden of Disease Study.[18] This was a one-time toll for the affected cohort. The remaining DWs (neonatal sepsis, CP) were from the Iran Burden of Disease Study[19] and the Dutch Burden of Disease study,[20] given that these were the only weights available and were previously used for an economic evaluation of neonatal sepsis in sub-Saharan Africa.[21]

All costs in foreign dollars were converted to US Dollars (US$) using OECD Purchasing Power Parity and inflated using the American Healthcare Consumer Price Index to present-day dollars in 2019.[22] US$ was chosen as it is the international dollar currency recognised by both government and non-governmental healthcare payers. The base case cost of the iNCK for distribution and biannual training for LHWs used in the model was US$10.25. The range of costs used for sensitivity analysis was based on the quoted estimate for mass distribution and production of the iNCK with LHW training (US$5) and initial start-up maximal costs (US$200).[6] Cost data for omphalitis-related hospital stay and outpatient care was obtained from the WHO.[16] Cost for outpatient antibiotics were provided by the Pakistan Drug Regional Authority, a Pakistan pharmacy source and a cross-sectional study of 1083 newborns with omphalitis in Karachi, Pakistan.[23–25] Treatment costs for mild/moderate omphalitis included antibiotic costs and either outpatient or hospitalisation costs for a 7-day treatment of a 4 kg neonate.[23–25] We did not assign a cost for standard care as we assumed that there would be no cost to the healthcare payer for interventions purchased privately by pregnant mothers. The cost of long-term sequelae to the healthcare payer was assumed to be 0 as these costs would be borne primarily by families. Finally, the only reported cost of outpatient treatment was in urban Pakistan and assumed to be the same for rural Pakistan.[26]

Patient and public involvement
Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Analysis
Base case analysis
The base case analysed assessed distribution of the iNCK to pregnant mothers at a cost of US$10.25 per kit with a CET of US$15.50 in comparison to standard care.

Sensitivity analyses
Deterministic sensitivity analyses were performed to assess parameter uncertainty and to identify threshold values for which the dominating strategy changed. Ranges for one-way sensitivity analysis were based on published literature or expert opinion. Variables with the greatest impact on the INMB in the one-way sensitivity analysis were assessed in the two-way sensitivity analysis.

Validation
Two programmers (KC and FM) screened the model for errors through manual review and using one-way

Table 1 Probabilities, costs and disability-adjusted life years used in the iNCK model

	iNCK distribution		Standard care		References
	Home delivery	Facility delivery	Home delivery	Facility delivery	
Probabilities					
Delivery site	0.40	0.60	0.39	0.61	Pell et al[6]
Use of iNCK (intervention) or standard of care (control)	0.95	0.90	0.18	0.72	Pell et al[6]
Any neonatal infection	0.15				Pell et al[6]
Relative risk of any neonatal infection given use of kit	0.55	0.73	1.17	0.93	Pell et al[6]
Relative risk of any neonatal infection given no use of any kit	0.96	0.92	0.96	0.92	Pell et al[6]
Severe infection given any infection and use of a kit	0.57		0.46		Pell et al[6]
Severe infection given any infection and no use of a kit	0.57		0.54		Pell et al[6]
Severe omphalitis given any omphalitis and use of a kit	0.47	0.39	0.29	0.35	Pell et al[6]
Severe omphalitis given any omphalitis and no use of a kit	0.47	0.39	0.32	0	Pell et al[6]
Mild/moderate omphalitis progressing to severe omphalitis	0.13				Muttalib and Morris, personal communication, 2018
Hospitalisation if omphalitis	0.10				Muttalib and Morris, personal communication, 2018
Hospitalisation if severe infection	0.50	0.57	0.50	0.57	Pell et al[6]
Death from sepsis given hospitalisation	0.33	0.22	0.33	0.22	Bhutta and Yusuf[31]
Death from sepsis given no hospitalisation	0.90				Muttalib and Morris, personal communication, 2018
Long-term sequelae	0.19				Ranjeva et al[21]
Death (annually)	0.001–0.23				WHO Life tables—Pakistan 2018
Death due to long-term sequelae annually	0.36				Yaqoob et al[17]
Costs (US$, 2018)					
Cost of LHW training per kit distributed	0.25		0		Muhammad et al, personal communication, 2019
Cost of the iNCK	10.00		0		Pell et al[6]
Cost of hospitalisation for sepsis	972.41				Hussain et al 2006
Cost of hospitalisation for omphalitis	192.52				WHO Pakistan, 2005
Cost of outpatient therapy (7 days)					
Cephalexin	16.42				Qamar et al[24]
Gentamicin	0.45				Qamar et al[24]
Penicillin	1.50				Qamar et al[24]

Continued

Table 1 Continued

	iNCK distribution		Standard care		References
	Home delivery	Facility delivery	Home delivery	Facility delivery	
Outpatient clinic visit	55.23				WHO Pakistan[25]
Total cost of outpatient therapy	73.60				
Health-related disability weights					
Cerebral palsy	0.17				Mathers et al[26]
Neurodevelopmental impairment	0.22				Ranjeva et al[21]
Sepsis	0.61				Naghavi et al[19]
Mild/moderate infection	0.01				Salomon et al[18]

iNCK, integrated neonatal care kit; LHW, Lady Health Workers.

sensitivity analysis of all variables. Face validity was verified through review by a content expert (SKM). Validating this model with goodness-of-fit measures was not possible given that existing research evaluations varied based on perspective,[27 28] time horizon,[28] intervention,[29] analysis[27–30] and outcome,[28 29] or a combination of these variables. Overall, these interventions were reported to be cost-effective based on their respective CETs, which was consistent with our results.[27–30]

RESULTS

Model parameters are illustrated in table 1.

Base case

Distributing the iNCK dominated the current standard of care because it is more effective and less costly, with lower expected DALYs (28.7 vs 29.6 years) at a lower cost (US$52.50 vs 55.20) per iNCK distributed, resulting in an INMB of US$10.22 at a CET of US$15.50.

These results were sensitive to the cost of the iNCK, baseline risk of infection and the estimated effect of the iNCK on the RR of infection (figures 2 and 3). As the baseline risk of infection increased, INMB associated with the intervention increased. The iNCK remained cost-effective for any iNCK cost up to US$25.90 (base case US$10.25). A two-way sensitivity analysis of iNCK cost and estimated effect of the iNCK on the RR of infection shows the dominance of iNCK (figure 2). As the estimated effect of the iNCK on the risk of infection decreases (up to RR 0.79), the cost of the iNCK must also decrease for the iNCK to remain cost-effective.

DISCUSSION

The iNCK was cost-effective compared with the current standard of care (INMB of US$10.22 at a CET of US$15.5). These results were most sensitive to the cost of the iNCK, baseline risk of neonatal infection and the RR of infection associated with use of the iNCK. At iNCK costs up to US$25.91 or RR of infection below 0.79,

the iNCK remained cost-effective. As the cost of the kit increased (up to US$105), a greater relative reduction in risk of infection (RR<0.79) was required for the iNCK to remain cost-effective. Thus, mass production of iNCK at a low cost and/or improving the effectiveness of the iNCK in reducing infection would be beneficial for the healthcare payer.

The main driver of cost-effectiveness in our model was reduction in risk of neonatal infection through use of the iNCK. This depended on a definition of severe infection revised by the cRCT authors in sensitivity analysis to optimise specificity. In a sensitivity analysis including the original definition of severe infection in the model, the iNCK
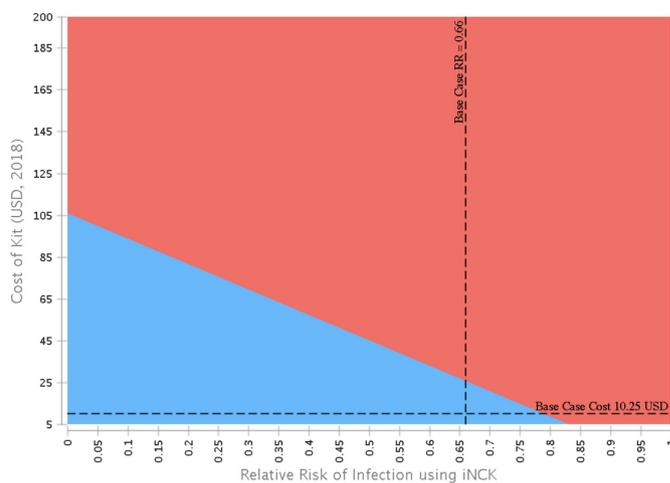
Figure 2 Two-way sensitivity analysis of iNCK cost versus relative risk of infection. The blue-coloured region represents ranges of the variables for which the intervention dominates, whereas the red-coloured region represents ranges of the variables for which standard care dominates. We note that as the estimated effect of the iNCK on the relative risk of infection decreases, a larger range of iNCK costs remain cost-effective. Similarly, as the cost of the iNCK decreases, a lesser reduction in relative risk of infection is required for the intervention to remain cost-effective. Base case values (RR: 0.66, cost US$10.25) are illustrated by the dotted lines. iNCK, integrated neonatal care kit; RR, relative risk.
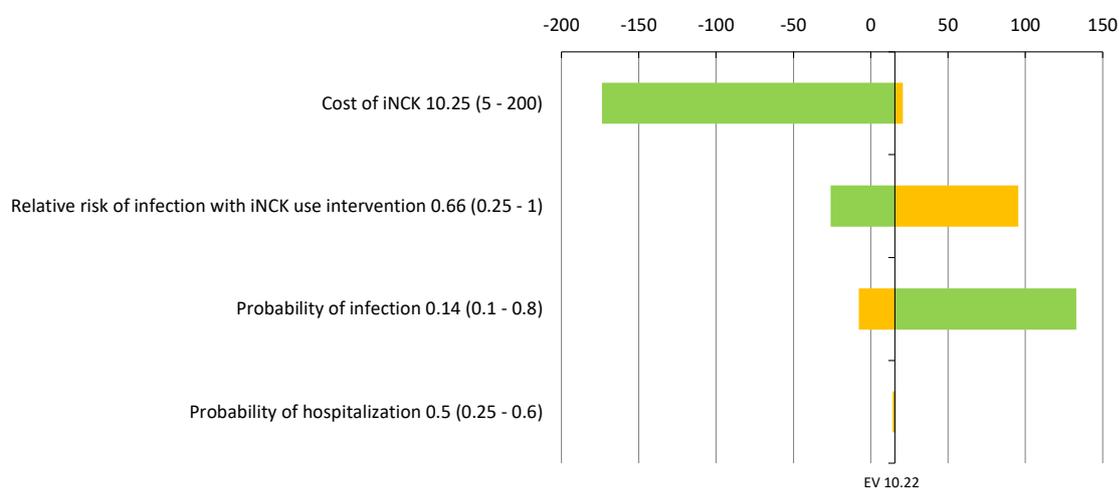
Figure 3 Tornado diagram of the impact of probabilities and costs on Incremental Net Monetary Benefit Comparing the Intervention to Standard Care. The X-axis represents the range of incremental net monetary benefit (INMB) when probabilities and costs are varied over the range displayed on the Y-axis at a cost-effectiveness threshold of US$15.50. The base case is represented by the vertical line with an INMB of US$10.22. Green bars represent increasing variable value above the base case value, orange bars represent decreasing variable value below the base case value. The model is most sensitive to the cost of the iNCK, baseline probability of infection and relative risk of infection. iNCK, integrated neonatal care kit; EV: Expected Value

was not cost-effective. The revised definition excluded the following variables: presence of abnormal activity and poor feeding. We elected to use this definition in our model as we aimed to capture the specific probability of severe infection while abnormal feeding and behaviour might reflect other non-specific causes of illness in the neonatal period, in particular when self-reported by caregivers rather than being observed by medical professionals. Retrospective recall by caregivers may have led to overidentification of possible severe infection in the cRCT using the abnormal feeding and behaviour criteria. The broad definition of severe infection was intended for high-sensitivity detection of illness in a community setting and not for specific identification of severe infection cases. For these reasons, the revised definition was retained in the final model. The lack of data in the cRCT including laboratory confirmation of serious bacterial infection or healthcare provider assessment of signs of possible serious bacterial infection are important limitations that must be addressed in future studies to inform cost-effectiveness analysis.

The most significant limitation of our model was lack of primary data and reliance on other published literature. Due to this limitation, our model may underestimate the cost-effectiveness of the intervention. For example, although the iNCK included tools for temperature monitoring and warming, we were not able to capture whether this contributed to improved neonatal outcomes. Similarly, clean birth practices may reduce the incidence of maternal infection and mortality; however, we could not evaluate the impact of iNCK use on maternal outcomes. Evidence of reduction in maternal sepsis-related morbidity and mortality as well as improved neonatal hypothermia detection and management would make the iNCK more

cost-effective. Finally, we were not able to evaluate whether correct use of the iNCK components was associated with greater cost-effectiveness. Based on a post-hoc definition, perfect compliance to all individual iNCK elements was 2%–3% within the intervention cohort.[6] We lacked data regarding how rates of infection may have differed between those with complete compliance compared with those with incomplete compliance to iNCK elements. While this likely represents real-world cost-effectiveness of the intervention, further study to evaluate the impact of compliance on risk of infection is needed. This would allow for additional sensitivity analyses to be conducted to determine how strategies to improve kit compliance may impact cost-effectiveness of the iNCK.

Additional data limitations did not result in significant effects on the cost-effectiveness of the intervention in sensitivity analysis. These included infection-specific mortality rates and costing data. First, infection-specific mortality rates were drawn from neonatal sepsis literature in urban Pakistan, not rural Pakistan.[31] While probability of death due to infection may be different in a rural setting, our model was not sensitive to a wide range of infection-specific mortality rates. Second, there were limitations in the published literature regarding cost data for LMICs. Although, wherever possible, we did use data from Pakistan, all of these data (cost of hospitalisation, cost of outpatient care) were from urban Pakistan. The cost of medications was based on weight of a 4 kg term neonate, which is likely an overestimate of average neonatal weight in Pakistan. Our model was not sensitive to a range of outpatient medication costs including zero, therefore costs associated with pursuing outpatient care were not a driver of cost-effectiveness in this model.

Our study findings require further validation to ensure generalisability. We assumed the use of existing healthcare

infrastructure and the LHW system to deploy the iNCK, increasing feasibility and limiting implementation costs. Thus, this cost-effectiveness study may not be generalisable to contexts without an established community health worker system. In addition, we assumed that healthcare was sought for all infants with infection. Data regarding healthcare-seeking behaviour and probability of hospitalisation were drawn from literature specific to Pakistan but included both rural and urban populations. Due to specific cultural beliefs and geographical constraints, barriers to seeking healthcare may be heterogeneous within a country and care-seeking in a rural setting may be diminished. If the number of infants who received care for infection was overestimated by our model, either in-hospital or as outpatients, the estimation of treatment-related costs would be excessive while infection-related mortality would be underestimated. We did not model the possibility that patients received no therapy at all given lack of available data; however, the probability of hospitalisation did not modify the cost-effectiveness of the iNCK in one-way sensitivity analysis. We relied on face validity with content experts to assess the accuracy of literature estimates.

Finally, we were unable to account for the effect of participation in a RCT in the control group on frequency of use of clean birth strategies, choice of location of delivery and surveillance for infection. It is well known that the Hawthorne effect[32] may impact the behaviour of enrolled participants, in this case biasing the control group towards use of clean birth strategies and decreased risk of infection. The iNCK was cost-effective despite frequent use of clean birth strategies in the standard care cohort. Thus, the benefit would likely be even greater in settings where clean birth practices are lacking.

With consideration of the stated limitations, our analysis indicates that distribution of the iNCK by LHWs in rural Pakistan is cost-effective at a conservative CET. These results are in keeping with published studies evaluating the cost-effectiveness of various clean birth strategies.[27 28 30] The cost per DALY averted for our base case was US$74 which compares favourably to other cost-effective interventions, such as rotavirus immunisation which is estimated to cost US$186 per DALY averted in South East Asia.[33]

CONCLUSION

This is the first study to evaluate the cost-effectiveness of the distribution of an iNCK by community health workers in rural Pakistan. With a conservative CET of 1% GDP per capita, the iNCK seems to be cost-effective at a cost of US$10.25 per kit and mean RR of any infection of 0.66. Further studies informed by additional primary and literature data are needed to validate these findings. Community distribution of an iNCK by community health workers may be a cost-effective government intervention to improve neonatal outcomes.

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