RETHINK PRIORITIES

Promising interventions in maternal and neonatal health

Global Health and
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Editorial note

This report was produced by Rethink Priorities between September and October 2024. The project was commissioned and supported by Open Philanthropy, which does not necessarily endorse our conclusions.

Our purpose is to inform Open Philanthropy's approach to funding in the maternal and neonatal health space. We do so by drawing on academic papers and reports, expert interviews with academics and practitioners, and preliminary BOTECs.

We have tried to flag major sources of uncertainty in the report, and are open to revising our views based on new information or further research.

We are grateful for the invaluable input of our interviewees. Please note that our interviewees spoke with us in a personal capacity and not on behalf of their respective organizations.

Executive summary

This report, commissioned by Open Philanthropy (OP), provides an initial exploration of maternal and neonatal health (MNH) interventions in low- and middle-income countries (LMICs) to identify promising areas for philanthropic investment.

Preventable maternal and neonatal deaths remain exceedingly high in LMICs. Across both mothers and newborns, conditions mapping onto the antenatal and intrapartum phases are responsible for the largest share of deaths and DALYs, suggesting that emphasis on these stages of pregnancy can lead to significant reductions in maternal and neonatal deaths. More specifically, for mothers, the leading causes of death are hemorrhage (27.1%), hypertensive disorders (14%), and sepsis (10.7%); for newborns, the leading causes of death are complications related to preterm birth (40%), followed by birth complications (34.1%), and neonatal sepsis (12.39%).

We spent roughly 2.5 weeks identifying maternal and neonatal interventions that could be deployed across the antenatal, intrapartum, and postpartum periods. We uncovered a total of 56 interventions by drawing from OP documents, four expert interviews, and desk research augmented by large language models (LLMs) and artificial intelligence (AI) tools. These interventions can be found in our longlist; the plurality of interventions target mother and child at the postpartum stage.

In coordination with OP, we selected three interventions for further investigation over a subsequent two-week period: basic emergency obstetric and newborn care (BEmONC), antenatal care, and injectable antibiotics for newborn sepsis.

Concerning basic emergency obstetric and newborn care (BEmONC)—a package of interventions that aim to reduce maternal and neonatal deaths during and immediately following childbirth—the Copenhagen Consensus recently undertook a LiST-based analysis that suggests a benefit-cost ratio of $83 per dollar spent on BEmONC, with neonatal resuscitation as the most cost-effective standalone intervention within the package. We centered our investigation on interrogating these cost-effectiveness numbers to understand whether the approach seems worthy of further consideration. We sense that these and other estimates may be optimistic based on our assessments of input data and methodologies deployed, but our conservative, low-confidence back-of-the-envelope calculation (BOTEC) nevertheless suggests that BEmONC is indeed quite cost-effective, with a social return on investment (SROI) of just under 2,400x. Our calculations can be found here.

We additionally conducted a rough BOTEC of neonatal resuscitation, an intervention included in the BEmONC package, and while we find it is quite cost-effective in our BOTEC, it has a much lower potential to save lives than would a more complete package of interventions. Additionally, we sense that the training costs for this intervention on its own would result in unattractive cost-effectiveness figures while neglecting to leverage a training program that could address a much greater health burden.

Next, we turned to antenatal care (ANC). Nearly all women around the world received at least one antenatal care visit (87%), but only 60% attended the minimum recommended visits established by the World Health Organization (WHO) (8). Our review of the evidence suggests that it might be more impactful to improve the quality rather than the overall number of visits. We build a package of interventions, or “must-haves”, that we would like to see occur during a single high-quality ANC visit. This includes: testing and treatment for hypertension and syphilis, as well as a tetanus vaccine and, depending on context, vitamin A supplementation. A conservative, low-confidence BOTEC suggests that such a package has an SROI of just 1,000x, though this is driven mostly by hypertension and Vitamin A supplementation.

Finally, we examined injectable antibiotics for newborn sepsis. In sub-Saharan Africa alone, about 5.29–8.73 million DALYs are lost each year as a result of neonatal sepsis. Expanding access to injectable antibiotics that can be administered in local community clinics or lower-level health facilities may be a particularly cost-effective way of addressing this burden, with some estimates showing the cost-effectiveness at roughly $17 per DALY averted. Digging into the literature, we find that quality evidence on the effectiveness of injectable antibiotics is actually poor. More recent evidence on AMR leads us to believe that the effectiveness of the recommended injectable antibiotics could be severely compromised, with no clear alternatives. Still, we conduct our own conservative, low-confidence BOTEC which suggests that injectable antibiotics appear to be highly cost-effective with an SROI of around 7,000x, though estimates change significantly (dropping to just above 2,500x) if gentamicin has substantially lost effectiveness in fighting infection.

In short, we believe that under a set of assumptions BEmONC and injectable antibiotics seem like particularly promising interventions to address maternal and neonatal health. We would recommend that OP conduct additional research to understand whether these are indeed good areas for philanthropic investment.

We conclude by reviewing several remaining uncertainties. One, a lot of the interventions we considered have large effects on stillbirths, and therefore on cost-effectiveness calculations. Excluding them from our models changes some conclusions significantly, but would be fairly straightforward to do. Including them also raises challenges, as both OP and GiveWell (GW) acknowledge uncertainties around the appropriate moral weights. Two, our BOTECs are highly sensitive to a series of assumptions regarding costs and effects. With additional time, we could have obtained more granular data on costs. With regard to effect, we are concerned that the LiST model, commonly used to gauge effectiveness, overstates the effectiveness of bundled interventions.

Finally, we are not confident we settled on the most promising intervention in the maternal and neonatal health space. Our longlist may suffer from gaps, and the interventions we selected for additional scrutiny might not, in fact, be the most promising among them. Of the interventions that stand out to us, at least two were mentioned by interviewees: (i) the establishment of milk banks and (ii) the provision of safe blood. We would recommend additional work to look at these and other relevant interventions in our longlist.

Purpose

This shallow report was contracted by OP to support their assessment of philanthropic efforts in the field of maternal and neonatal health (MNH). Our focus is on two questions:

1. What are the types of interventions delivered in LMICs to address maternal and neonatal health?
    a. Are there interventions to improve maternal and neonatal health outcomes that OP has not previously investigated?
2. What are the 3 to 4 most tractable and neglected interventions in this space?
    a. How strong is the evidence that they work?
    b. How cost-effective are they, based on existing cost-effectiveness analyses?

By answering these questions we aim to inform OP's approach to MNH, including deprioritizing research or grants on the basis of limited evidence, elaborating on key cruxes and conducting additional research to resolve these, as well as identifying new funding opportunities.

This report represents an initial phase of exploration into this critical area of global health and reflects the efforts of two researchers working over five weeks. Our main deliverables are two: 1) a longlist of interventions (details of which are enclosed in this document), and 2) three deeper investigations into three shortlisted interventions: basic emergency obstetric and newborn care (BEmONC), antenatal care, and antibiotic injections for newborn sepsis. Alongside these reports, we present preliminary BOTECs.

The remainder of the document is structured as follows: First, we briefly introduce the topic of MNH. Second, we propose an analytical categorization of the stages of pregnancy and associated conditions. Third, we conduct a brief overview of the burden of disease in terms of deaths and DALYs across mothers and newborns. Fourth, we discuss our approach to building the longlist and briefly review the logic of shortlisting interventions. Finally, we turn to a deeper discussion of each of these three shortlisted interventions.

Maternal and neonatal health is a significant global issue

Close to 300,000 women die every year from causes related to pregnancy and childbirth[1], with 85% to 97% of these deaths occurring from preventable causes (90% confidence interval).[2] These deaths are also geographically concentrated: ~52% of them occur in 13 countries experiencing very high levels of maternal mortality rates (MMR), defined as 500 or more deaths per 100,000

[1] See *Trends in maternal mortality 2000 to 2020* (WHO, 2023): estimates by WHO, UNICEF, UNFPA, World Bank Group, and UNDESA/Population Division.

[2] We have some uncertainty over the precise share. Most documents we examined suggested that most deaths are preventable, but did not explicitly settle on a number. To estimate a number, we took a WHO (2014) fact sheet on maternal mortality that states that "Every day, approximately 800 women die from preventable causes related to pregnancy and childbirth." We multiply 800 deaths by 365 days to arrive at a point estimate of the number of preventable maternal deaths every year (approximately 292,000). If there are 300,000 maternal deaths a year, then the preventable share is given by 292,000/300,000 or .97. This seems a bit high so we use this as an upper bound. To get a floor, we lower the number of daily maternal deaths to 100–though we doubt the true discrepancy is this large–and multiply by 365 days, then divide by total number of maternal deaths to arrive at an estimate of 0.85. We have high confidence (80%) that the true number is somewhere in this range.

deliveries.[3] Indeed, according to UNICEF (2024a), roughly 70% of maternal deaths are concentrated in sub-Saharan Africa.

Similarly, according to UNICEF (2024b), nearly 2.3 million children die each year within their first 28 days of life[4], and at least 80% of these deaths are from preventable causes.[5] The top 13 countries identified by levels of neonatal mortality rate (NMR) account only for ~16% of all neonatal deaths, illustrating that the relationship between mortality rate and concentration of deaths isn't the same across mothers and children.[6] Still, 99% of neonatal deaths occur in low- and middle-income countries (Milton et al., 2022).[7]

Across mothers and children, conditions mapping onto the antenatal and intrapartum phases are responsible for the largest share of deaths and DALYs

There are three stages of pregnancy that map onto interventions and specific conditions: antenatal, intrapartum, and postpartum

Maternal and neonatal health issues and associated interventions occur during three stages of pregnancy: antenatal, intrapartum, and postpartum. We apply this categorization to map interventions to the conditions and diseases that affect mother and child. The antenatal stage encompasses the entire period from conception to the onset of labor, involving fetal development and maternal physiological adaptations. The intrapartum stage covers active labor and delivery, culminating in the birth of the baby and placenta. Finally, the postpartum stage spans the 28 days following childbirth, characterized by maternal recovery and newborn adaptation. Several diseases and conditions map onto these stages, and we use this categorization to help make sense of their relative importance in the subsequent discussion.

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[3] To arrive at 52%, we scraped maternal mortality trend data—which capture estimates from WHO, UNICEF, UNFPA, World Bank Group, and UNDESA/Population Division—into our spreadsheet on Global Maternal and Newborn Mortality Estimates (WHO, 2023). We then categorized countries estimated to have a maternal mortality rate (MMR) of 500 or higher per 100,000 as experiencing very high levels of MMR, using a definition provided by a 2024 paper in The Lancet (Souza et al., 2024). These 13 countries are: South Sudan, Chad, Nigeria, Central African Republic, Guinea-Bissau, Liberia, Somalia, Afghanistan, Lesotho, Guinea, Democratic Republic of the Congo, Kenya, and Benin (in this order). We have not sought subnational data, but it is our sense that–if such data exist–they may be helpful in further narrowing the geographies that should be targeted for interventions.

[4] See the *Neonatal deaths* tab in our Global Maternal and Newborn Mortality Estimates for which we have scraped data on estimated neonatal deaths generated by the UN Inter-agency Group for Child Mortality Estimation in 2024 (UNICEF, 2024b).

[5] See page 2 of UNICEF's document on Ending preventable newborn deaths and stillbirths by 2030: "We know the causes of 80% of newborn deaths and have solutions to address them and prevent lifelong disability (3). 80% of all newborn deaths result from three preventable and treatable conditions: complications due to prematurity, intrapartum related deaths (including birth asphyxia) and neonatal infections. Proven, cost-effective, interventions exist to prevent and treat each of these main causes of death."

[6] We could not identify a source defining what a high level of NMR would be. In the absence of this information, and for comparison with MMR, we simply chose to estimate the share of all deaths that came from the 13 countries with the highest NMR. To do so, we scraped data from a 2019 article in The Lancet that estimated comparable NMRs for all countries in the world (Hug et al., 2019); the data come from Table A.5 in the Supplementary appendix. We sorted countries by NMR, identified the top 13, and added their total deaths. These 13 countries are: Pakistan, Central African Republic, South Sudan, Somalia, Lesotho, Guinea-Bissau, Mali, Chad, Mauritania, Côte d'Ivoire, Sierra Leone, Nigeria, and Benin.

[7] See this 2022 article in The Lancet (Milton et al., 2022): "...with LMICs bearing the burden of 99% of global neonatal mortality."

For mothers, the leading causes of death are hemorrhage, hypertensive disorders, and sepsis

We conducted a quick literature search to understand the main causes of deaths and DALYs for mothers and children. Concerning mothers, a 2014 publication in The Lancet estimates that hemorrhage (27.1%), hypertensive disorders (14%), and sepsis (10.7%) were responsible for more than half of maternal deaths worldwide between 2003 and 2009 (Say et al., 2014). To confirm the rough order of importance, we downloaded data from the Global Burden of Disease Study 2021 (IHME, 2021) and sorted by deaths and DALYs. Table 1 describes these data.[8] In line with the article in The Lancet, hemorrhage is the leading cause of maternal mortality (24.52%), followed by hypertensive disorders (19.96%), other direct maternal disorders (14.45%)[9], and sepsis and other infections (9.24%). By contrast, the leading causes of DALYs are other direct maternal disorders (24%), sepsis and other maternal infections (20.06%), late maternal deaths (14.06%), and maternal hemorrhage (9.29%).

[8] We have some uncertainty over these numbers, which stems from the discrepancy in total number of deaths reported by the GBD and the estimates available from the WHO's *Trends in maternal mortality 2000 to 2020*, with the latter being much higher (WHO, 2023). We have not spent time examining the source of the discrepancy, though we are assured that the rough order matches with the 2014 article in *The Lancet*.
[9] "Other direct maternal disorders" in IHME (2020) include various conditions, the most common six of which are: obstetric embolism; maternal care for other conditions predominantly related to pregnancy; complications of the puerperium, not elsewhere classified; other complications of labour and delivery, not elsewhere classified; malignant neoplasm of placenta; and maternal care for other foetal problems. We have not looked at the distribution of these disorders within the broader category, but we can form a view of their relative importance by dividing the total category by the top six conditions–assuming they are equitably distributed–to suggest that each might account for roughly ~2.4% of all deaths or 4% of DALYs. This seems to us quite small relative to the order disorders.

Table 1: Share of Deaths and DALYs Across Maternal Disorders Ordered by the Stage of Pregnancy for Intervention, 2021

Cause	Share of deaths	Share of DALYs
Antenatal	**32.07%**	**26.09%**
Maternal hypertensive disorders	19.96%	8.67%
Maternal abortion and miscarriage	8.74%	8.18%
Ectopic pregnancy	3.37%	9.23%
Intrapartum	**30.63%**	**12.51%**
Maternal hemorrhage	24.52%	9.29%
Maternal obstructed labor and uterine rupture	6.11%	3.22%
Postpartum	**12.17%**	**34.12%**
Maternal sepsis and other maternal infections	9.24%	20.06%
Late maternal deaths	2.92%	14.06%
Multiple	**25.14%**	**27.28%**
Other direct maternal disorders	14.45%	24.00%
Indirect maternal deaths	10.03%	2.70%
Maternal deaths aggravated by HIV/AIDS	0.66%	0.58%

Note. Data from Global Burden of Disease Study (IHME, 2021); calculations our own (see here).

For newborns, the leading causes of death are premature birth, asphyxia or trauma, and sepsis

Concerning newborns, the World Health Organization (2024c) reports that the leading causes of death are premature birth, birth complications (birth asphyxia/trauma), neonatal infections, and congenital anomalies–though they provide no specific numbers. UNICEF's report on *Ending Preventable Newborn Deaths and Stillbirths by 2030* (WHO & UNICEF, 2020, p. 2) states that the former three causes are responsible for 80% of all neonatal deaths. Like above, we turned to the GBD 2021 to obtain data on newborn deaths and associated DALYs for 2021. We present these data in Table 2. In line with the literature reviewed, the leading cause of death is complications related to preterm birth (40%), followed by birth complications (34.1%), and neonatal sepsis (12.39%) The shares for the leading causes of DALYs are the same. We return to these data when explaining our approach to the shortlist.

Table 2: Share of Deaths and DALYs Across Neonatal Disorders Ordered by the Stage of Pregnancy for Intervention, 2021

Cause	Share of deaths	Share of DALYs
Antenatal: *Neonatal preterm birth*	**40.02%**	**40.02%**
Intrapartum: *Neonatal encephalopathy (birth asphyxia and trauma)*	**34.10%**	**34.09%**
Postpartum	**14.07%**	**14.07%**
Neonatal sepsis and other neonatal infections	12.39%	12.39%
Hemolytic disease and other neonatal jaundice	1.68%	1.68%
Multiple: *Other neonatal disorders*	**11.81%**	**11.82%**

Note. Data from Global Burden of Disease Study (IHME, 2021); calculations our own (see here).

Longlisting maternal and neonatal interventions

To longlist maternal and neonatal interventions, we reviewed OP documents, undertook four expert interviews, and conducted desk research augmented by LLMs and AI tools

We conducted a shallow landscaping exercise over two weeks to identify and briefly assess existing interventions that improve maternal and neonatal health outcomes, with a focus on low- and middle-income countries. We did not aim to fill out every cell but rather relied on the sources described below to include the information that was available. As a result, many cells are empty but could potentially be filled by conducting additional research. We identified a total of 59 interventions that have not been deeply researched by either OP or GW. To do so, we looked at the following sources:

1. **Resources shared by OP:** We first drew from existing OP documents shared by the cause prioritization team, identifying all interventions and adding them to the longlist. Given that these interventions were already known to OP, we conducted no further research into them. However, if we encountered additional detail on these interventions as we conducted other research, such as cost-effectiveness estimates or reports that discussed these interventions, we added the source document to that row under the Notes column. In a few cases, we also added interventions mentioned within the shared documentation that were not the primary focus of the documentation.[10]
2. **Interviews**: We talked to five individuals across four organizations. We added any and all interventions they mentioned to our longlist. We spoke with:
    a. Meika Ball, Senior Research Associate at GiveWell (GW);
    b. Andrew Storey, Senior Director, Maternal and Neonatal Health, and Marta Prescott, Director, Analytics and Implementation Research, at the Clinton Health Access Initiative (CHAI);

[10] For instance, GiveWell (2022) mentions several interventions it has investigated in the "Evidence on effect of practices promoted"section of its *Facility-Based Maternal and Neonatal Health Interventions* report.

c. Joy Lawn, Professor of Public Health at the London School of Hygiene and Tropical Medicine; and
d. Lara Vaz, Senior Program Director at the Population Reference Bureau.

3. **Large language models:**
   a. We conducted searches using large language models (LLMs). Specifically, we asked Gemini and ChatGPT to answer variations of the following question: "What are the top interventions to lower maternal and neonatal health deaths in low and middle-income countries?" We spent roughly one hour trying to phrase these prompts differently and collecting output, stopping once the LLM search only returned interventions already identified in the first step and/or that were out of scope.[11]
   b. We conducted a Google and LLM search for global MNH reports. We identified two specific reports—World Bank (2016) and UNICEF (2023)—that we used to provide additional context for this report and to help identify promising interventions. Specifically, we searched for key terms, including variations of "maternal neonatal health global report" and deployed variations of the following prompt on Gemini and ChatGPT: "Please identify all key global reports on maternal and neonatal health causes." We spent a few hours searching for these reports, identifying key sections, and populating our longlist.
4. **Elicit:** We conducted two searches on Elicit, one of which resulted in primarily systematic reviews[12] and the other primarily in publications of relevant randomized controlled trials (RCT).[13] We then selected several pieces of information ('columns') that we deemed relevant for Elicit to populate for each paper, then downloaded the resulting spreadsheets and compiled them in a Google Sheet. For all papers published in 2014[14] or later, we quickly reviewed the intervention information provided by Elicit (primarily scanning Elicit's intervention description, intervention effects, and main findings columns in the first two sheets here) and added interventions to the longlist that were not yet present. For the RCT-specific search, we only added interventions that were not yet mentioned in the longlist and that demonstrated promising effects on MNH.
5. **Additional resources we encountered**: In conducting our research we also identified helpful tables in two papers estimating the cost-effectiveness of maternal and neonatal

[11] As an example of the output, Gemini returned the following in response to the question, "What are the top interventions to lower maternal and neonatal health deaths in low and middle-income countries?": **Quality antenatal care**: Providing at least four antenatal visits with skilled healthcare providers for essential health assessments, screenings, and interventions, such as:

- Tetanus toxoid immunization
- Screening and treatment for syphilis and other STIs
- Malaria prevention and treatment
- Iron and folic acid supplementation
- HIV testing and treatment
- Blood pressure monitoring and management of hypertension
- Identification and management of high-risk pregnancies

Since quality antenatal care was already on the longlist, we did not add this to the longlist.

[12] The prompt entered into Elicit was as follows: "Which interventions are most effective in reducing maternal and/or neonatal health or DALYs? Please prioritize papers with strong evidence (i.e. randomized controlled trials or other experimental methods, systematic reviews, meta-analysis)." It resulted in 16 hits, three of which were published before 2014.

[13] The prompt entered into Elicit was as follows: "Show me all randomized controlled trials testing interventions that aim to reduce maternal and neonatal mortality in low- and middle-income countries." It resulted in 24 hits, 16 of which were published before 2014.

[14] We decided to focus on papers published in the last 10 years given that we had identified a review of MNH intervention cost-effectiveness published in 2014. We thought this review would likely cover most of the promising interventions from the Elicit-identified papers that were published pre-2014.

health interventions: Mangham-Jefferies et al. (2014) Tables 2 and 3, and Memirie et al. (2019) Tables 1 and 4.[15]

a. We scraped the data from these tables and added them to separate sheets in the longlist spreadsheet (e.g., see here).
b. We added all interventions from Memirie et al. (2019) to the longlist since their list was quite brief.
   - We included only the intervention description and DALY estimate for these entries since these were available in Tables 1 and 4.
c. We added all interventions from Mangham-Jefferies et al. (2014) that contained a cost-effectiveness figure in terms of cost per death or DALY in Table 2, and where the "quality" of the study was deemed "High" by the authors in Table 3.
   - In addition to the paper's estimate(s) of cost-effectiveness, Tables 2 and 3 contained intervention descriptions, evidence information (type, geography, effect magnitude), and the author/year of the relevant study–all of which we added to the associated columns in the longlist.
d. On several occasions, the interventions in these papers were related to others in the longlist, though were not exactly the same (e.g., some cases were due to intervention bundling). In those cases, we created a dropdown for the intervention in the longlist to include information from these papers on the relevant cost-effectiveness numbers.

We identified 56 maternal and neonatal interventions of possible interest to OP, with the plurality of interventions targeting mother and child at the postpartum stage

Our longlisting led to the identification of 56 interventions, details of which can be found in our spreadsheet. Table 3, below, shows the distribution of the longlisted interventions by the stage of pregnancy during which it would be delivered and whether it targeted the health of the mother, child, or both. Our interventions are balanced across mother and child, with most interventions targeting both. With regard to the stage of pregnancy, a plurality of interventions deal with postpartum care, followed by intrapartum intervention and those that target multiple stages.

[15] We identified Mangham-Jefferies et al. (2014) in our Elicit search and Memirie et al. (2019) in our broader desk research.

Table 3: Distribution of Longlisted Intervention by Stage of Pregnancy and Target Individual

Stage of Pregnancy	Mother	Child	Both	Total
Antenatal	3	6	0	9
Intrapartum	4	2	7	13
Postpartum	2	5	10	17
Multiple	7	3	3	13
Other	*0*	1	3	4
Total	16	17	23	56

Note. Data from our longlist.

Shortlisting

We proposed a process to shortlist interventions (available in the appendix). Our approach yielded 21 interventions and initiated a conversation with OP aimed at narrowing the list down to 3-4 interventions for further examination. A 30-minute discussion ultimately led us to identify three interventions that correspond to the antenatal, intrapartum, and postpartum stages, respectively: antenatal care, basic emergency obstetric and newborn care (BEmONC), and injectable antibiotics for newborn sepsis. The basis of selection did not end up following strict criteria, but OP mentioned also being interested in selecting at least one packaged intervention (that did not include kangaroo mother care [KMC]).

Once selected, we conducted a sense check of our interventions based on burden. We noticed that we had mostly centered on interventions with effects on a) newborns or b) newborns and moms, which aligned with the 8:1 ratio of newborn to maternal deaths (i.e., we should probably weigh interventions that save newborn lives more heavily). The vast majority of newborn deaths occur before postpartum, and there are seemingly few interventions in the antenatal stage capable of preventing preterm births—with the exception of antenatal care. We discussed adding neonatal resuscitation as a standalone package, but subsumed our discussion of this intervention into BEmONC (as it is a component of that package). Table 4 provides an overview of these interventions, which we explore in turn below.

Table 4: Summary information on shortlisted interventions

Name	Stage	Description	Packaged interventions	Cost-effectiveness estimates
Basic emergency obstetric and newborn care (BEmONC)	Intrapartum and immediate postnatal	Provision of training and resources to enable delivery of obstetric and newborn care services in facilities in LMICs	• Clean birth environment • Immediate drying and additional stimulation • Thermal protection • Clean cord care • Uterotonics • Controlled cord traction and removal of placenta • Parenteral administration of anticonvulsants and antibiotics • Antibiotics for preterm or prolonged premature rupture of membranes • Assisted vaginal delivery • Neonatal resuscitation • Removal of retained products of conception • Labor induction for pregnancies lasting 41+ weeks • Antenatal corticosteroids for preterm labor	\$53-\$55/DALY averted or \$1,497 per life saved (Willcox et al., 2017) \$83 (benefit-cost ratio from Madise et al., 2023)
Antenatal care	Antenatal	Care provided by healthcare professionals to pregnant women to ensure the best health conditions for both mother and baby during pregnancy	• Healthy eating counseling • Nutrition education • Balanced energy and protein dietary supplementation • Iron and folic acid supplements • Iron and folic acid supplements • Calcium supplements • Vitamin A supplements • Restricting caffeine intake • Anemia • Asymptomatic bacteriuria (ASB) • Intimate partner violence (IPV) • Gestational diabetes mellitus (GDM)	-

			• Tobacco use • Substance us • Human immunodeficiency virus (HIV) • Syphilis • Tuberculosis (TB) • Symphysis-fundal height (SFH) measurement • Ultrasound scan • Antibiotics for asymptomatic bacteriuria (ASB) • Preventive anthelmintic treatment • Tetanus toxoid vaccination • Malaria prevention: intermittent preventive treatment in pregnancy (IPTp) • Pre-exposure prophylaxis (PrEP) for HIV prevention	
Injectable antibiotics for newborn sepsis	Postpartum	Administration of injectable antibiotics (gentamicin) as an outpatient treatment for infection	• Gentamicin (IM) alone or in combination with amoxicillin (oral)	$17 (per DALY averted from Memirie et al., 2019)

Basic emergency obstetric and newborn care (BEmONC)

Our goal in this section is to provide a high-level understanding of potential cost-effectiveness as it relates to the basic emergency obstetric and newborn care (BEmONC) package of interventions, both through providing an overview of relevant literature, as well as through our own back-of-the-envelope calculations. BEmONC refers to the provision of training and resources to enable the delivery of emergency obstetric and newborn care services within facilities in LMICs. The interventions within the package aim to avert maternal and neonatal deaths during and immediately following childbirth, including intrapartum stillbirths. Two early interviews pointed to emergency obstetric care (Prof. Joy Lawn) and several interventions within the package, such as neonatal resuscitation and clean cord care[16] (Prof. Joy Lawn and Dr. Lara Vaz), as promising.

Overall, we think BEmONC shows significant promise and is a good candidate for further research and consideration as OP evaluates grantmaking opportunities in maternal and neonatal health.

[16] Prof. Lawn additionally mentioned delayed cord clamping.

LiST analysis suggests a benefit-cost ratio of $83 per dollar spent on BEmONC, with neonatal resuscitation as the most cost-effective standalone intervention, and assisted vaginal delivery and antenatal corticosteroids accounting for the majority of lives saved if implemented in isolation

The Copenhagen Consensus recently undertook LiST-based cost-effectiveness analyses of several MNH interventions, both as independent interventions and as packages grouped according to multiple interventions' ability to be administered at the same time (Madise et al., 2023).[17] The report identified a package of interventions associated with basic emergency obstetric and newborn care (BEmONC) as highly cost-effective relative to other interventions or packages, with an estimated benefit-cost ratio of $83 per dollar spent.[18] They argue that such a package stands out due to the historically high number of women giving birth in facilities worldwide, which leverages the "challenging and costly work of building sufficient infrastructure, hiring staff, and incentivizing women to have facility births" (p. 23). Additionally, they argue the costs per life saved are low given that the bundle comprises inexpensive procedures (delivered via nurses and midwives as opposed to more expensive doctors) and can address a range of life-threatening (primarily) intrapartum conditions. The evidence we have reviewed supports this narrative, suggesting that a low-dose high-frequency training intervention in Ghana led to health impacts that translate to an estimated $53/DALY (Willcox et al., 2017; Gomez et al., 2018).

The package of interventions recommended in the Copenhagen Consensus report[19]–grouped loosely based on our understanding of the type of condition it aims to address–is as follows:

- **Infection prevention:** clean birth environment, clean cord care, parenteral antibiotics, and removal of retained products of conception (e.g., placental fragments)
- **Neonatal survival:** immediate drying and stimulation of the newborn, thermal protection, neonatal resuscitation, antenatal corticosteroids for preterm labor
- **Hemorrhage protection:** uterotonic drugs, manual removal of the placenta
- **Other:** parenteral anticonvulsants (prevent eclamptic seizures), assisted vaginal delivery (multiple possible maternal and neonatal benefits), induction of labor for pregnancies lasting 41+ weeks (reduce risk of stillbirth and primarily neonatal complications in 5% of pregnancies)

For each intervention in the package, we include the costing assumptions used in the Madise et al. (2023) report alongside the lives saved estimates from Friberg and Weissman (2020)—a

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[17] Broadly, the methodology in the Copenhagen Consensus report divides monetized benefits by costs across the 59 LMICs with the highest maternal mortality and morbidity (Friberg and Weissman, 2020, p. 20). Benefits include averted mortality and morbidity and, in some specifications, benefits from demographic dividends (e.g., effects on income per capita) and treatment costs averted. Costs include intervention costs (drugs/supplies), staff and supervisor salaries, costs to women seeking care (e.g., travel, productivity), and incentive costs for demand stimulation. Training costs are not included.

[18] Note that the report identifies BEmONC + Family Planning as the most cost-effective package, with a cost-benefit ratio of $87.

[19] "Clinical content" covered in the training sessions in Gomez et al. (2018) is similar though it includes KMC. Altogether, it includes the following: "respectful maternity care, infection prevention and control, clinical decision-making, evidence-based support of normal labor and birth (including use of the partograph and active management of the third stage of labor), immediate newborn care, newborn resuscitation, antenatal corticosteroids for anticipated preterm labor, management of severe pre-eclampsia and eclampsia, management of postpartum hemorrhage (including repair of lacerations), prevention and treatment of maternal and newborn sepsis, kangaroo mother care, and data collection and use / reporting of data" (p. 3, Table 2). Thus, the interventions included within the package are highly similar, though not entirely consistent across sources.

previous Copenhagen Consensus report preceding the more current version—in [this sheet](). Of the estimated 1.84 million lives saved annually—an estimate that uses the LiST tool, with which we have some reservations and therefore treat these estimates as an upper bound (see [Appendix]())[20]—1.42 million are attributable to just three interventions: assisted vaginal delivery (908K lives saved, of which 722,000 or 80% are averted stillbirths), antenatal corticosteroids for preterm labor (357,000 lives saved), and neonatal resuscitation (152,000 lives saved). All others are expected to save <100,000 lives per year, though some of these interventions are extremely cheap, with costs as low as $0.53 per newborn for immediate drying and stimulation.

Of the interventions responsible for averting the most deaths, neonatal resuscitation stands out as particularly cost-effective, with unit costs of just $4.45, whereas commensurate costs for assisted vaginal delivery and antenatal corticosteroids are almost 8x the cost at $32.64 and $31.73, respectively. [Friberg and Weissman (2020)]() find the benefit-cost ratio of neonatal resuscitation in averting deaths is $757 (followed by antenatal corticosteroids at $138; p. 6, Figure 1),[21] with a cost per life saved of less than $1,000 (p. 14, Table 3). While Friberg and Weissman's analysis suggests that all other BEmONC interventions evaluated are below $4,000 per life saved (except for induction of labor in regards to post-term pregnancies, for which an estimate is not provided), "controlled cord traction/removal of placenta" stands out as least cost-effective at $41,000 per (maternal) life saved, while also saving a relatively small share of lives annually (12K) relative to other interventions in the package. However, it is unclear to us what portion of the cost associated with any BEmONC program is attributable to training efforts and equipment against any particular intervention, so leveraging the fixed costs of the training program to avoid such deaths may still be worthwhile.

The Copenhagen Consensus analysis aims for target coverage of 90%, though we are highly skeptical that the resources—in particular, the skilled birth attendants and the equipment—as well as the use of facilities for giving birth are sufficient to reach the targets they seek. Moreover, and critically, their benefit-cost ratio does not account for the costs of training skilled birth attendants in the emergency obstetric and newborn care interventions within the BEmONC bundle.

Thus, while the exercise seems useful to provide a crude comparison of the potential benefits of various interventions and packages, we are not confident that the estimates are grounded in the realities associated with the implementation of those interventions and packages. We therefore turn our attention to a study that aims to assess the treatment effects and cost-effectiveness of a BEmONC training in Ghana.

[20] Despite our reservations, the differences in lives saved across interventions are so sufficiently stark that we assume the majority of lives saved are indeed attributable to these three interventions. However, with more time, we would replicate the LiST modeling to check whether the order that interventions are added to the bundle makes a difference to the lives saved estimates.

[21] The authors use a value of a statistical life approach to calculate the benefits of lives saved in USD, which we did not critically review: "To put a dollar value on the lives lost we used the approach recommended in the Reference Case Guidelines for Benefit-Cost Analysis in Global Health and Development. We used the current Value of a Statistical Life in the US (of roughly $10 million per life saved in 2018 dollars), which we then converted to different country-specific values based on the PPP GNI per capita relationship of the respective countries to the US" (p. 22).

Evidence from a cluster RCT suggests ~$55 per DALY averted and ~$1,500 per life saved from low-dose high-frequency BEmONC training program in Ghana

Gomez et al. (2018): Cluster RCT in Ghana

The best evidence we identified in this area in a non-exhaustive search (~15 minutes on Google Scholar when searching for interventions on SBA training programs) is from a cluster randomized trial in Ghana that ran from 2014-2017 (Gomez et al., 2018). When asked about BEmONC, Meika Ball from GW suggested there might be a lack of clarity around "what fundable programs people have in mind when they talk about BEmONC" and has assumed they relate to essential newborn care training programs, specifically referencing Gomez et al. (2018), which gives us some confidence that this study is the most appropriate for in-depth review.

The study's motivation highlights that SBAs are present at the majority of births in Ghana (68%), though half of under-5 deaths in Ghana are newborn deaths and half of newborn deaths take place on the first day of life, suggesting deficiencies in intrapartum and immediate postpartum SBA care. The study therefore randomly assigns a "low-dose high frequency (LDHF) training approach on long-term evidence-based skill retention among SBAs" to 40 hospitals in order to assess the relative risk of intrapartum stillbirths and 24-hour newborn deaths during months 1-6 and months 7-12 of training. The authors designed the training based on a literature review defining features of effective training. The LDHF training approach involves two 4-day sessions at the facility where SBAs receive mentoring (onsite and/or by mobile phone), SMS quizzes and reminders, and weekly practice opportunities using simulators and models (as well as daily lunches). The approach differed from the ongoing BEmONC training in Ghana at the time of the study, which lasted up to 10 days and took place offsite. The authors claim the latter approach does not "foster a team-centered approach" and only includes a few SBAs from any given facility.

Claims around causal inference appear to come from 'pipeline randomization' over four waves that allowed for comparison of treated and untreated facilities as the program was being rolled out, though we did not come across any discernible analysis comparing outcomes across waves and most analysis seems to be pre-post. Moreover, stratification based on three regional and four caseload categories meant that the waves were unbalanced, which we flagged but did not scrutinize further due to time constraints. Moreover, staff in participating facilities were aware of the trial (i.e. it was not blinded) in addition to the outcomes of interest, so the possibility of experimenter effects cannot be ignored. In total, 403 SBAs enrolled and 201 were available at the time of knowledge assessment one year after the intervention.

The risk of newborn mortality within the first day of birth fell by 59% after the first low-dose training (i.e. within the first six months) and 70% after the second low-dose training (months 7-12) relative to the six-month pre-intervention period, while the risk of intrapartum stillbirth fell by 36% and 52% over the same periods, respectively.[22] Average scores on the objective structured clinical examination (OSCE)—which appears to be a common metric used to assess relevant clinical knowledge—increased ~30% (p<0.001) after a year. The authors suggest that newborn deaths somewhat steadily declined month to month, while stillbirths declined

[22] The adjusted relative risk of 24-hour newborn mortality in hospitals where SBAs were offered the LDHF training was 0.41 (p<0.001, 95% CI 0.32-0.51) and 0.30 (p<0.001, 95% CI 0.21-0.43) in the first and second six-month periods of the trial, respectively. For intrapartum stillbirths, the adjusted relative risk was 0.64 (p<0.001, 95% CI 0.53-0.77) and 0.48 (p<0.001, 95% CI 0.36-0.63) in the first and second six-month periods of the trial, respectively.

immediately and remained low throughout the study period. Much of the identified effect on *stillbirths* appears related to neonatal resuscitation,[23] while the authors attribute the decline in *newborn deaths* to newborn care interventions (e.g., KMC) and identification and management of asphyxia. The authors argue the approach is sustainable given that training SBAs across entire facilities provides opportunities to "reinforce learning and build a system of checks and balances," while allowing for continued mentorship and practice opportunities (e.g., via simulators), as well as enabling opportunities for skills transfer to new SBAs as they join facilities.

Willcox et al. (2017): Cost-effectiveness of low-dose high-frequency BEmONC training program

Willcox et al. (2017)[24] conduct a cost-effectiveness analysis based on the study results above in which they claim the LDHF approach saved 544 lives at a cost of $1,498 per life saved or $53 per DALY averted compared to no training.[25] Probabilistic sensitivity analysis using Monte Carlo simulations resulted in just under $55 per DALY averted, with a 100% probability that the cost per DALY averted is under Ghana's GNI per capita in 2015, which was $1,480.

Costs include development costs (e.g., personnel and editor time to adapt the BEmONC curriculum), startup costs (e.g., training for health information officers and mentors), and implementation costs (e.g., training and follow-up costs, such as transportation, personnel, lunches, training materials, and the like). The vast majority of costs are related to implementation (96%). Additionally, the costs include all operational costs, such as building space and utilities. In short, the included costs appear quite comprehensive and representative of the possible costs associated with the program. Likewise, the sources of these costs (e.g., various financial records and interviews) appear to be reliable.

The authors make some modeling choices that should be checked for consistency with OP's internal approaches. For instance, the authors do not impose age weighting when translating estimated lives saved to DALYs, whereas OP does. The authors also assume 28.2 DALYs per estimated death averted, whereas OP assumes 43 (32) DALYs per death averted for under 1-year-olds (over 5-year-olds). Moreover, OP does not discount health effects, while the authors impose a 3% discount rate "so as to discount health effects at the same rate as costs" over the three-year analytic time horizon (p. 5). Overall, the authors' assumptions suggest an underestimation of benefits relative to the assumptions underlying OP's assessments of cost-effectiveness, leading us to believe that cost-effectiveness may be quite a bit higher than estimated in Willcox et al. (2017).

Furthermore, the authors claim omission of YLDs from their analysis is both practical (given most health impacts from newborn mortality are from years of life lost) and leads to a slightly

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[23] "... [S]ince resuscitation was attempted for all nonmacerated newborns not breathing at birth, many babies who would otherwise have been declared intrapartum stillbirths but actually had intrapartum-related asphyxia, were successfully resuscitated corroborating the assertion by Wall et al. that training SBAs in newborn resuscitation could prevent up to 30% of mortality in full-term babies due to intrapartum-related events" (Gomez et al., 2018, p. 7). LiST counts these as 'newborn lives saved' rather than 'stillbirths averted' (i.e., 152,000 newborn lives saved—and not stillbirths averted—attributable to neonatal resuscitation).

[24] Two of the original study authors (Patricia Gomez and Amos Asiedu, both from Jhpiego) co-authored the cost-effectiveness analysis in Willcox et al. (2017), which had six authors in total. If the authors of the original study had interest in promoting the LDHF approach or research, it somewhat calls into question the true unbiasedness of the results.

[25] The deterministic sensitivity analysis that led to these figures suggested a best-case to worst-case range based on use of exclusively low-end and high-end parameters of $19-$149 per DALY averted (p. 6).

conservative estimation of impact. Similarly, they assume that rolling out the program via a local partner or government would cost less than the incremental cost Jhpiego encountered, though they use the latter and thus claim their estimates may also be conservative in this way. Based on discussions with the LDHF team at Jhpiego, they believe the cost per provider trained could decrease by about 44% (from $901 to $506) within the Ghanaian health system, based on efficiencies and expected cost changes.

Two features of the LDHF training stand out to us as important in ways that could further improve impact, thereby improving cost-effectiveness. First, Prof. Joy Lawn recommended focusing on interventions that improve team-based performance. LDHF seems likely to improve interactions and teamwork within facilities, in particular relative to offsite trainings that do not encourage SBAs to work together. In follow-up communication, Prof. Lawn suggested a need for LDHF training beyond just SBAs and extending to the full team, including doctors, nurses, and others (for instance, biomeds), and for the need to track change and drive quality improvement using innovative data dashboards. Second, at least one expert mentioned the issue of low retention among facility workers. To the extent that career advancement opportunities and one's own and one's peers' work competency improve workplace satisfaction, we imagine such a program could improve retention. However, if the program improves the prospects for increasingly skilled labor to seek better-paying opportunities outside of Ghana, it may have unintended effects on retention.

A BEmONC BOTEC suggests that this bundled intervention could represent a promising grantmaking opportunity for OP

We spent a few hours constructing a crude BEmONC back-of-the-envelope calculation (BOTEC; see here) on OP's request. Generally, we aimed to identify inputs directly from the literature reviewed in this section (primarily the Copenhagen Consensus reports, where relevant data was most readily available) and otherwise looked for data that are broadly representative of LMICs. With more time we would likely aim to identify particular countries or sub-national regions to which we could tailor the BOTEC to ensure we are using consistent input data.[26]

In our BOTEC, we first estimate the number of DALYs averted each year. Due to time constraints, we use LiST estimates of lives saved ("deaths averted") and apply a significant discount ("haircut") to provide a more conservative estimate of deaths averted annually. We apply this haircut given our concerns around the non-additive nature of LiST's burden estimates (see discussion in Appendix). That said, this parameter is one of our two main uncertainties that can significantly influence the bottom line, and we encourage OP to adjust this parameter in line with its own perspective on the LiST estimates. We then use OP's assumption of 43 DALYs per death averted to convert stillbirths and neonatal deaths averted to DALYs averted, and 32 DALYs per death averted to convert maternal deaths averted to DALYs averted.

[26] Note that the cost estimates from the Copenhagen Consensus, which we use in our BOTEC, come with similar caveats: "Although we present these results in aggregate, each country will need to take into account the state of its health system when assessing the potential impact of these packages. In some settings, the staffing required to provide the interventions may be in place, while the medications and drugs might be in short supply, while in others, the opposite may be true. Both situations will affect the potential number of lives that can be saved as they will affect either the quantity or the quality of the intervention or package delivered. Any shortfalls in staff, drugs or supplies needed will either make it difficult for a country to achieve the 90% target coverage rate or reduce the quality and thus the impact of the intervention provided" (Friberg and Weissman, 2020, p. 18).

To calculate costs, we attempt to calculate costs per facility birth of training SBAs in BEmONC and of the drugs/supplies, staff, hospital, and supervision costs associated with each individual intervention in the BEmONC package. In calculating the cost of training per birth, we divide the total cost of implementation of the BEmONC training (as estimated in Willcox et al., 2017) by three to get an annual cost, then divide this total by the total number of births in a year in the Gomez et al. (2018) study. To calculate the additional costs associated with each individual intervention, we multiply the intervention-specific cost estimates in Table A1 of Madise et al. (2023) by the estimated number of additional women receiving treatment due to the increase in coverage. Our second main uncertainty pertains to this increase in coverage, as the Copenhagen Consensus reports suggest an approach that increases country-level coverage to 90% but where baseline coverage varies significantly, as confirmed in Alemayehu et al. (2023).[27]

Using OP's valuation of a DALY at $100,000, as well as a number of other uncertain assumptions and inputs, we calculate the social return on investment (SROI) of BEmONC to be over 2,300x (including stillbirths averted[28]), which is slightly lower than Lauren's three-hour estimate of 2,600x.[29] However, our SROI is sensitive to several uncertain parameters in the BOTEC, so we provide this tool as a starting point for OP to explore and improve over time.

The BOTEC mechanics are such that the cost-effectiveness declines the lower the current coverage. Specifically, the benefits are static (i.e., pulled directly from Friberg and Weissman, 2020) while the costs are dynamic, depending on the assumed baseline level of coverage across the entire study population. In reality, we might expect benefits to decline with time, assuming the regions in most need are targeted first, while the costs may also decline with learning and information sharing across regions and countries. The extent to which cost-effectiveness changes would depend on the relative speed at which costs and benefits decline.

With more time, we would conduct additional research into the inputs in our BOTEC and/or apply the BOTEC to a particularly promising country or region, i.e. countries with high burden, a high proportion of facility births, and many SBAs or midwives working in those facilities. Additionally, we would conduct probabilistic uncertainty analysis to better understand the mechanics of the model as well as the impact of uncertainty on the ultimate SROI estimate, with a focus on understanding the importance of particular uncertain parameters on the output and reducing uncertainty around the most impactful parameters.

[27] "Utilization/Crude Coverage of EmONC Services Of the 32 reviewed studies, 13 reported the crude coverage (use) of the EmONC services. It ranged from 3% in 2011 in Ethiopia to 73% in 2016 in Togo. Studies from Ethiopia and Nigeria reported a high unmet need for EmONC services in which 3%, and 3.9% of women with obstetric complications were treated at fully functional EmONC facilities in Ethiopia and Nigeria, respectively, varied significantly by the sub-national administrative structures. The national EmONC assessments from Ethiopia, Sierra Leone, Ghana, Malawi, and Gambia reported that 18%, 20%, 34%, 51%, and 56%% of women with obstetric complications were treated at health facilities, with a significant disparity by the sub-national administrative structures.
Four studies have also shown a progressive improvement in EmONC service utilization. A study from Mozambique reported that the EmONC service utilization increased from 20% in 2007 to 26% in 2012.25 A Nigerian study also reported a threefold increase in EmONC service utilization (3.3% to 9.9%) within three years (2012 to 2015). In the same study, the percentage of women who sought care outside health facilities dropped significantly from 8.3% to 3.2%. Furthermore, studies from Cameroon and Burkina Faso also reported an increasing trend in EmONC service utilization" (Alemayehu et al., 2023).
[28] Giving no weight to stillbirths leads to a SROI under the same specifications of just under 1,400x.
[29] We have not seen this BOTEC, but rather received a note that Lauren had done such a BOTEC and landed on 2,600x in the project brief OP shared for the project.

Neonatal resuscitation appears cost-effective on its own, but would only achieve a fraction of the lives saved, and estimates in the literature overlook training costs

Given OP expressed interest in neonatal resuscitation as a standalone intervention, we adapted the BEmONC BOTEC to focus exclusively on neonatal resuscitation. We update the cost and deaths averted estimates to focus specifically on neonatal lives saved[30] in our BOTEC—reducing the haircut on the lives saved estimate from LiST, since we are no longer bundling interventions. We additionally arbitrarily assume training costs are halved by the need to train on only one skill–since training time would decline significantly–but several of the fixed costs of training would remain. Making these updates suggests a SROI of over 4,800x in the model.

Similarly, Stenberg et al. (2021)'s WHO-CHOICE analysis for eastern sub-Saharan Africa and Southeast Asia—which also relies on LiST—suggests that neonatal resuscitation is the most cost-effective intervention among a number of MNH interventions analyzed. However, we were skeptical of their estimation approach. First, similar to the Copenhagen Consensus, they do not include training costs in their analysis. This omission seems critical given Gomez et al. (2018)'s point that intrapartum and immediate postpartum maternal and neonatal deaths remained high in Ghana despite almost 7 in 10 births now being overseen by a skilled birth attendant. Moreover, Stenberg et al. (2021) use a "generalized cost-effectiveness" approach that compares intervention implementation to a "null" scenario with no historical investments (as opposed to an incremental cost-effectiveness approach that expands on a country's current practices[31]). They also assume well-functioning health systems where the standard is to follow best practices, which will not reflect realities in a number of high-need countries and regions. Finally, they consider a 100-year time horizon, which assumes a level of program sustainability as well as future population and global health predictability that seems unlikely given the myriad ways in which growth, migration, innovation, education, and the like may alter intervention need, cost, and effects. We also note that many of the high-burden countries identified earlier in the report are not included in the regions the authors consider.

Finally, despite the promising cost-effectiveness numbers in Stenberg et al. (2021) and in our rough BOTEC, the number of potential lives saved declines quite dramatically when considering neonatal resuscitation on its own (i.e., to 152,000 neonatal lives across 59 LMICs, according to LiST) relative to a package of interventions. Given the fixed costs associated with large-scale training efforts—for instance, training mentors, creating program materials, and transporting training facilitators to healthcare facilities—it seems likely that training on a package of interventions would be more cost-effective and save many more lives than coordinating a training program for neonatal resuscitation alone. If neonatal resuscitation would not require the extent of training as the full collection of interventions in the BEmONC package does (e.g., if an instruction pamphlet is sufficient), then we may be convinced that providing the equipment and instructions for neonatal resuscitation is a more cost-effective approach than BEmONC. However, GW noted that "discussions with one [organization] implied that training would be too expensive to be [cost-effective]", so they were not prioritizing neonatal resuscitation programs in the near term. Thus, it seems likely that

[30] Note that while the LiST estimates used in the Copenhagen Consensus reports suggest that neonatal resuscitation averts neonatal deaths (and not stillbirths), Gomez et al. (2018) suggest that neonatal resuscitation is the main driver of stillbirths averted, highlighting the blurred line between intrapartum stillbirths and deaths in the first hour of life.
[31] With more time, we would read O'Day and Campbell (2016) or related sources to expand on issues with the generalized approach.

neonatal resuscitation is only cost-effective to implement if bundled with training on a number of additional inexpensive and effective interventions.

Antenatal care

The World Health Organization (2016) defines antenatal care (ANC) as the "care provided by skilled health-care professionals to pregnant women and adolescent girls in order to ensure the best health conditions for both mother and baby during pregnancy" (p. 1). Two main themes, which we refer to as the frequency and quality questions, guided our initial exploration of this intervention:

1. Frequency: What does ANC take-up look like in LMICs? How difficult is it to increase the number of visits to the recommended number?
2. Quality: What seem to be the most cost-effective components of ANC? How can we optimize visits to get the highest impact per visit?

Nearly 40% of women do not complete the WHO recommended number of antenatal visits, though we assess the evidence leading to such recommendation to be weak

In 2016, the World Health Organization (2018) updated its recommendation[32] on the number of ANC visits from 4 to 8.[33] The shift reflected emerging evidence that the fewer visits were associated with increased perinatal deaths–stillbirths and early neonatal death up to 7 days of life.[34] According to Gebeyehu et al. (2022), almost 49% of women in sub-Saharan Africa attend the minimum recommended number of visits under the previous recommendation (4), with 35% attending once and 13% receiving no visits.

Nearly all women around the world received at least one antenatal care visit (87%), but only 60% attended the minimum required visits.[35] Since the number of visits has become an important indicator of antenatal care, we undertook a quick review of the most recent available evidence on how the frequency of visits is associated with maternal outcomes. To do so, we ran a series of queries by Consensus and Elicit to generate papers since 2010 that assessed the effects of the frequency of ANC visits on maternal and neonatal mortality. The papers we gathered are available in this spreadsheet.

In general, the quality of the evidence is weak, with a single RCT study among the 10 papers collected in our search. The WHO-sponsored RCT (Dowswell et al., 2015) and its reanalysis (Vogel et al., 2013) show that a reduced number of ANC visits is associated with an increased

[32] "The GDG, emphasizing the evidence indicating increased fetal deaths and lesser satisfaction of women with the four-visit model (also known as focused or basic ANC), decided to increase the recommended number of contacts between the mother and the health-care providers at time points that may facilitate assessment of well-being and provision of interventions to improve outcomes if problems are identified (see Recommendation E.7 in Table 1)" (WHO, 2016, p. x).
[33] The WHO (2016) recommendation splits these contacts as follows: one contact in the first trimester, two contacts in the second trimester, and five contacts in the third trimester.
[34] See Dowswell et al. (2015) and Vogel et al. (2013).
[35] In sub-Saharan Africa this is as low as 49% attending the minimum recommended visits, 35% attending once, and 13% receiving no visits.

risk of stillbirth, though this result is reported as being "borderline for statistical significance",[36] and had no statistically significant effects on neonatal or maternal mortality. Concerning non-experimental evidence, since women who seek ANC care may differ on many characteristics from those who do not (e.g., they may be on average more prone to complications), we do not take conclusions from the non-RCT studies at face value.

With regard to the rest of the non-experimental evidence, the remaining 8 papers are suggestive of a link between ANC and maternal and neonatal outcomes. One of three papers reporting maternal outcomes showed a positive association between ANC visits and a reduction in maternal mortality, and three[37] out of five papers reporting on neonatal outcomes showed a positive association between ANC visits and a reduction in neonatal mortality (Ahmed and Mohamed, 2018). With regards to maternal outcomes, two additional studies[38] show positive associations between ANC visits and non-death outcomes, including giving birth in a health facility and reduced postpartum complications. In sum, low-quality evidence suggests there might be some positive link between ANC visits and maternal and neonatal outcomes.

Taken together, we think that there is a significant gap in our understanding of how the frequency of visits impacts maternal and neonatal health. We also don't think that the WHO recommendations are on strong scientific footing; basing global recommendations on one set of studies for which a pooled result shows an adverse outcome that is "borderline for statistical significance" strikes us as overly cautious. From our perspective, this would mean not discarding approaches that have fewer touchpoints with pregnant women. While it may be true that more visits could be better, we take the view that the content of those visits, even if they are few, have potential to shape the trajectory of the pregnancy, and the health of both mother and child. In short, we think getting women from 0 to 1 visits may be more impactful than moving from 3 to 4. Moreover, it is our impression that what constitutes ANC varies significantly across and within countries, which we confirm to be true in the next section. Given these conclusions and insights from Douglas Chukwu,[39] we deprioritized further research into the question of frequency and turned to quality.

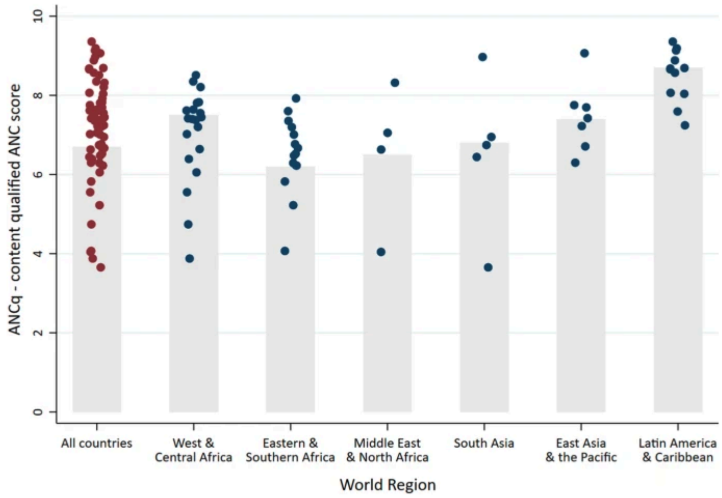
[36] Technically, they show effects on perinatal deaths (which include the first seven days of life), but evidence shows that what is driving these results are increases in fetal death in a specific range: "Stratification of fetal deaths by gestational age (22 – 27, 28 – 31, 32 – 36 and >36 weeks) showed a statistically significant increase in fetal deaths between 32 to 36 weeks of gestation (Adj RR 2.24; 95% CI 1.42, 3.53), the other periods were not significantly different between the comparison groups" (Vogel et al. 2013)

[37] See Doku and Neupane (2017), Tekelab et al. (2019), and Tesfay et al. (2023).

[38] See Corrao et al. (2020) and Berhan and Berhan (2014).

[39] In our correspondence, Douglas Chukwu agreed that "frequency vs. quality is a great way to think about ANC, and ideally we'd want to improve both" while leaning "significantly more towards the second option, which would mean standardizing and maximizing the potential health benefits of any contact with the healthcare system." He caveated that "some interventions have to be spaced out, like intermittent preventive treatment (IPT) in pregnancy for malaria which is recommended at 16-18 weeks and at least a month apart, but there are some updates in recognition of issues with access."

Figure 1: Antenatal Care Quality (ANCq) Scores for 63 Countries



ANCq means for 63 LMICs, by UNICEF regions. The gray bars show the region weighted median for the countries with data. Source: DHS and MICS, 2010–2017

Note. ANCq mean scores for 63 LMICs, by UNICEF. Figure from Arroyave et al. (2021).

The quality of ANC varies significantly across and within countries, with wealthier women receiving the highest quality care

In our quick review of the literature,[40] it appears that there are significant quality concerns regarding antenatal care across low- and middle-income countries, with the poorest and more disadvantaged groups receiving the lowest quality care.[41]

First, there is substantial heterogeneity with regard to the implementation of antenatal care both across and within countries. Concerning cross-country variation, a 2021 study deploys a content-qualified ANC coverage indicator called ANCq to compare the quality of ANC in 63 countries (Arroyave et al., 2021).[42] This study finds that there is as much as a 6-point spread (out of a maximum of 10) between countries, with the largest spreads in Africa and South Asia; similarly, the lowest average scores are found in those two regions, see Figure 1. A related global study of 91 countries in The Lancet shows that there are significant gaps in the quality of ANC: close to a third of all pregnant women did not have their blood pressure, urine, or blood checked at any point during the entire pregnancy (Arsenault et al., 2018). Figure 2, drawn from that same study, shows that substandard ANC is concentrated in countries in sub-Saharan Africa, South Asia, and Southeast Asia.

Figure 2: Quality of Antenatal Care in 91 LMICs

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[40] We spent roughly 2 hours conducting desk research to understand basic quality differences in the provision of ANC. We quickly came to the conclusion that differences within and across countries are both relevant to targeting ANC.

[41] By low-quality care we mean visits that lack basic services. What studies define as low quality varies. Arsenault et al. (2018) discuss three essential services: blood pressure monitoring, and urine and blood testing, whereas Arroyave et al. (2021) use 10 indicators (including the frequency of visits.)

[42] The ANCq indicator is slightly problematic because it partly conflates frequency with quality. More specifically, the indicator is measured "as a score, composed of seven variables which add points to the score: first visit in the first trimester of pregnancy (1 point), at least one visit with a skilled provider (2 points), total number of visits (1 point for 1–3 visits, 2 points for 4–7 visits, and 3 points for 8 or more visits), blood pressure measured (1 point), blood sample collected (1 point), urine sample collected (1 point), and receiving at least two shots of tetanus toxoid (1 point)" (Arroyave et al., 2021).

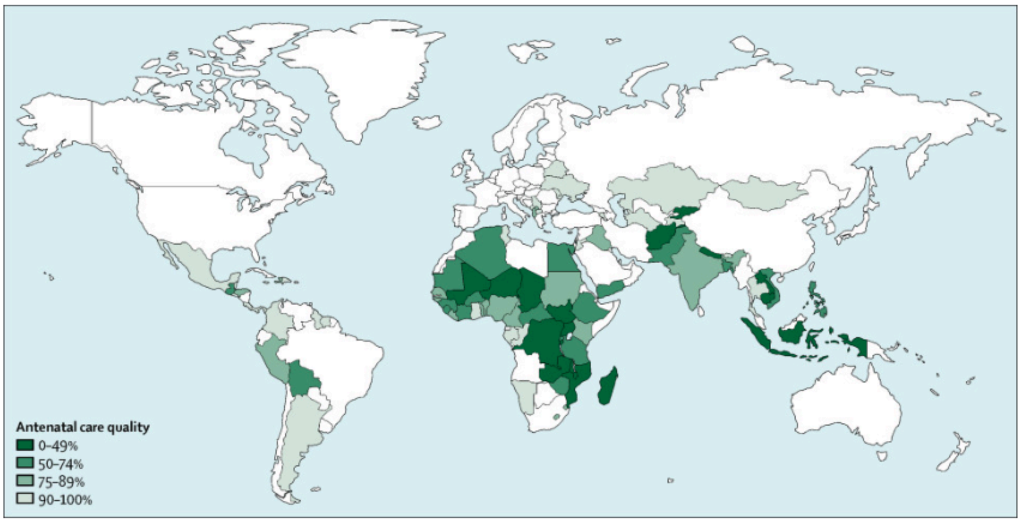


Figure 1 Antenatal care quality in 91 low-income and middle-income countries

Note. Non-colored regions had no data available or were not relevant to this analysis. Antenatal care quality is defined as the proportion of women who report blood pressure monitoring, as well as urine and blood testing at any point during the pregnancy (among those who had at least one visit with a skilled provider). Source: Arsenault et al. (2018)

At the same time, there is significant within-country variation. A study in India shows that the quality of antenatal care, defined as including essential physical examinations and services,[43] was significantly better in southern states than in northern Indian states (Rani et al., 2007). A 2016 study using DHS data for Bangladesh, Cambodia, Cameroon, Nepal, Peru, Senegal, and Uganda shows that within countries, ANC coverage and quality[44] depends on geographical location (Saad-Haddad et al., 2016).

Second, within countries, socioeconomic status appears to be a key determinant of any difference in the quality of ANC received. For example, the 2018 Lancet study described above finds that, on average, the wealthiest women were 4x more likely to report high-quality care when compared to the poorest women (and this effect is more than doubled for wealthy women in low-income countries; Arsenault et al., 2018). According to a 2015 observational study in Nigeria, a very small share of the population (4.6%) receives high-quality ANC, but women in the richest quintile are 3.5x more likely to receive high-quality ANC than those in the poorest quintile (Fagbamigbe & Idemudia, 2015).

The most cost-effective interventions targeting antenatal care have to do with maternal assessment, based on our review of the evidence

Given heterogeneity in the quality of antenatal care across LMICs, it is not entirely clear how to assess the cost-effectiveness of ANC. It is likely, for instance, that any effectiveness data will be overstated, and any cost data will be understated, in those places where ANC is least

[43] Including: "measurement of weight, height, blood pressure; urine and blood testing; abdomen examination; provision of iron/folic acid supplementation and tetanus toxoid immunization; and provision of information on nutrition, danger signs of pregnancy, delivery care, newborn care and family planning" (Rani et al., 2008, p. 63).
[44] Defined as: "blood sample taken, blood pressure taken, urine sample taken and being told about pregnancy problems" (Saad-Haddad et al., 2016)

accessible.[45] For example, effectiveness data may take for granted the facilities of high-income countries; moreover, the costs of providing care probably rise if one operates in more remote locations. Thinking specifically about these contexts, we think it is worthwhile to identify those key components of ANC that should occur if, for example, a woman attends a single antenatal care visit.

We approach this in two ways. First, we review WHO recommendations on ANC, breaking down ANC by component interventions to identify those pieces that seem the most cost-effective. Second, we draw on our desk research to match these components to cost-effectiveness estimates. An important caveat is that we do this on the basis of data that is collected for many countries. It seems reasonable to us that one might want to adapt this package on the basis of specific geography. More research would be needed to provide these tailored recommendations.

In 2016, the World Health Organization published the *WHO Recommendations on Antenatal Care for a Positive Pregnancy Experience,* a comprehensive guide for women about routine ANC (WHO, 2016). We compiled relevant ANC interventions[46]in this spreadsheet. We time-capped the amount of time we spent looking for cost-effectiveness papers for each of our 24 interventions to about 2 hours, noting that we pulled in information for 9 interventions from a previously identified source.

Table 5 summarizes the cost-effectiveness in cost per death averted for interventions grouped in terms of whether they addressed nutrition, maternal assessment, or preventative measures. In general, while there is significant heterogeneity across interventions within a given bundle, the maternal assessment interventions have the lowest cost per death averted. Thus, in thinking about the ideal first visit ANC, we suggest that it should include, at a minimum, blood and urine work and other diagnostic tools to identify and treat hypertension and syphilis. Looking at seemingly particularly cost-effective interventions in other categories, we think including a tetanus vaccine and vitamin A supplements (in certain contexts) should also be offered in the earliest visits. In sum, our recommended package of “must-have” interventions if pregnant women were to have a single ANC visit includes: testing and treatment for hypertension and syphilis, as well as a tetanus vaccine and, depending on context, vitamin A supplementation.

[45] Moreover, there doesn’t appear to be any good cost-effectiveness data from LMICs on antenatal care. We spent roughly 1 hour conducting desk research on this issue, googling variations of: “cost effectiveness of antenatal care maternal death low income countries”. We did not come across any papers published after 2010 that addressed costs in LMICs and that used maternal mortality as an outcome.
[46] Health system strengthening was explicitly out of scope for this project, given ongoing, separate Rethink Priorities research into the topic.

Table 5: Average Cost Effectiveness by Intervention Types

Intervention type	Interventions included	Average cost per death averted in thousands of US$ (lowest; highest individual CE)
Nutritional interventions	Balanced energy and protein dietary supplementation, iron and folic acid supplements, calcium supplements, vitamin A supplements	$50 ($17-$80)
Maternal assessment	Hypertension management and treatment, syphilis, HIV	$45.67 ($13-$63)
Preventative measures	Tetanus toxoid vaccination, malaria prevention: intermittent preventive treatment in pregnancy (IPTp), pre-exposure prophylaxis (PrEP) for HIV prevention	$88.67 ($5-$209)

Note. This table used only interventions for which we identified cost-effectiveness estimates. Most of these numbers are from the Copenhagen Consensus report (Madise et al., 2023), making most of them comparable. The exception is the HIV effectiveness number, which makes it difficult to compare in the context of the other interventions. For sources on numbers, see our spreadsheet.

We also discussed antenatal care in correspondence with Meika Ball on October 3, 2024. Ball similarly modeled the combined benefits of intervention, including tetanus vaccination, intermittent preventive treatment in pregnancy (IPTp) to prevent malaria, interventions to treat HIV, and increases in facility birth rates. We exclude malaria in part because it is expensive and context-specific.

A BOTEC on a basic ANC package for a single visit suggests that such intervention might have an SROI below 1,000x, though we are highly uncertain about this number

We spent a few hours constructing a crude ANC BOTEC that relies on many of the same assumptions and inputs of our BEmONC BOTECs, see here. We test the cost-effectiveness of our “must-have” package as outlined above.

To do so, we gather DALYs directly from Friberg and Weissman (2020) and adjust them according to OP preferences. To calculate the share of additional women covered by such a program, we identify the number of women of reproductive age and multiply by the share of those who give birth each year across 59 LMICs. We estimate the number of women receiving good quality ANC at 63.42%.[47] We then set the target of good ANC coverage to 90% to align with Copenhagen Consensus DALY estimates.

Using OP's valuation of a DALY at $100,000, as well as a number of other uncertain assumptions and inputs, we calculate the social return on investment (SROI) of a "must-have" ANC package to be right below 1,000x. We note that this return is largely being driven by stillbirths averted. As to the interventions themselves, in our model, hypertension and vitamin A supplementation are doing most of the effectiveness work–a package considering only these two interventions has a much more favorable SROI of around 1,500x. As before, the model results also hinge on how much we think LiST is overstating the effects of the bundled interventions. If it is not, the SROI of a must-have ANC package looks much more favorable, almost doubling to right under 2,000x.

With more time, we would have looked at more comparable costs for a bucket of LMICs and dug into the possible cost efficiencies of offering these interventions together.

Injectable antibiotics for newborn sepsis

Neonatal sepsis is a significant cause of death among newborns. Estimates from Fleischmann et al. (2021) set the burden at almost 3,000 incidents of sepsis per 100,000 live births, of which roughly 18% lead to death–the vast majority of which occur in LMICs. In sub-Saharan Africa alone, a 2018 paper estimates that 5.29–8.73 million DALYs are lost each year as a result of neonatal sepsis (Ranjeva et al., 2018).

In this section, we consider instead injectable antibiotics as an outpatient intervention to fight infection in newborns. The World Health Organization (2015) recommendations for treatment for newborn infection include referral to a hospital for treatment and use of two antibiotics: 1) penicillin or 2) ampicillin (oral) plus gentamicin (IM). However, the WHO's standard recommendations around treatment for newborn sepsis assume access to more advanced healthcare facilities, namely hospitals. This may be unreasonable in some settings and for various reasons. In sub-Saharan Africa, for example, a 2022 paper shows that only ~43% of women have access to healthcare facilities (Tessema et al., 2022).[48]

Acknowledging this reality, WHO (2015) published *Managing Possible Serious Bacterial Infection in Young Infants When Referral Is not Feasible*, a report outlining best practices related to treating infection in cases where families refuse or cannot access hospital treatment. Specifically, WHO guidelines support the use of gentamicin (IM) and amoxicillin (oral) in first-level health facilities or community facilities. In practice, outpatient treatment requires community health

[47] We draw on Gebeheyu et al., (2022), which suggests that 13% of women in sub-Saharan Africa receive no ANC, and on Arsenault et al. (2018), which implies that 27.9% of those that do receive bad quality ANC (defined as not having their blood pressure, urine, or blood checked at any point during the entire pregnancy). We combine as follows: adding the share of women with no ANC care (13%) and weighing the remainder (87%) by the bad quality factor (87*27.1 =23.6%). We add these percentages together: 13+23.6 = 36.6 to estimate the share receiving bad care. We estimate the share receiving good care as 1-0.37= 0.63, which is our estimate of current coverage.

[48] Not having access is defined by a composite variable: "We generated a composite outcome variable using each country's DHS standard question. The questions included the following:

- Getting the money needed for treatment (big problem/not a big problem).
- Distance to a healthcare facility (big problem/not a big problem).
- Having to take transport (big problem/not a big problem).
- Not wanting to go alone (big problem/not a big problem).

The responses to the questions asked are 'big problem' and 'not a big problem'. If a woman faces at least one problem, access to healthcare is considered a big problem and is coded 1 or 0 otherwise" (Tessema et al., 2022).

workers (CHWs) to have the required training to diagnose, administer, and follow up on a newborn's condition, which may be challenging to obtain in low-resource settings (Duby et al., 2019). In this section, we try to focus on the provision of gentamicin alone, though it is hard to know whether papers that mention injectable antibiotics do so as well (and not in combination with oral antibiotics.)

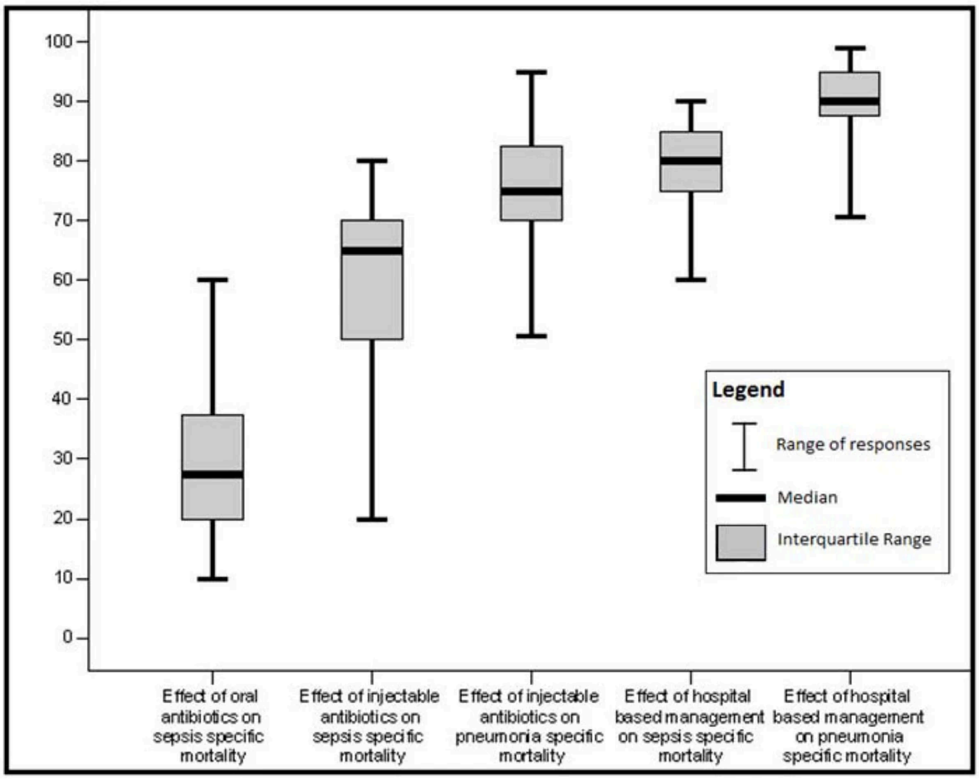
High-quality evidence on the effectiveness of injectable antibiotics is lacking, but experts estimated in 2010 that their effectiveness hovers around 65%; given AMR we think these numbers are too optimistic

The evidence around the effectiveness of injectable antibiotics is fairly weak.[49] LiST estimates on effectiveness of this intervention rely on a 2011 review paper (Zaidi et al., 2011) that, finding insufficient rigorous evidence, uses expert opinion to estimate the effectiveness of different types of management for sepsis, see Figure 3. According to experts, the average effect of injectable antibiotics on sepsis is ~65%. Along these lines, a 2018 systematic review found evidence to support the use of gentamicin (IM) and amoxicillin (oral) for treating neonatal sepsis when hospital care is unavailable (Fuchs et al., 2018).[50] We do not have a sense of how well-calibrated these estimates are, but, as we discuss below, we are highly skeptical that these numbers hold true today.

We did find credible evidence from a 2015 RCT (Baqui et al., 2015) conducted between 2009 and 2013 in Bangladesh that evaluated different types of outpatient regimens against each other, including using injectable antibiotics exclusively. Recruitment of patients was restricted to infants with one clinical sign of severe (but not critical) infection whose parents refused hospital admission. Patients were then randomized to one of three treatment arms testing combinations of injectable and oral antibiotics (one regimen including only injectables).[51] All three treatment arms had similar death rates within seven days of enrollment (~10%), suggesting that injectable antibiotics alone are roughly as effective as combinations of injectable and oral antibiotics, at least when it comes to non-severe cases of infection. Given this evidence, we would be interested in learning more and comparing the practical challenges of delivery of injectables only compared to combinations of injectables and oral antibiotics, but we have not done this research.

[49] Namely, it appears that ethical concerns make it impossible to use RCTs to compare the effects of receiving certain types of antibiotic management compared to none among vulnerable populations (Zaidi et al., 2011).
[50] See: "In conclusion, current WHO guidelines which support the use of gentamicin and penicillin for inpatients or gentamicin (IM) and amoxicillin (IM, per os) when admission is not possible accord with currently available evidence and other international guidelines, and there is no strong evidence to change this guidance" (Fuchs et al., 2018, p. 513).
[51] The treatment arms were: "The standard treatment was intramuscular procaine benzylpenicillin and gentamicin once per day for 7 days (group A). The alternative regimens were intramuscular gentamicin once per day and oral amoxicillin twice per day for 7 days (group B) or intramuscular procaine benzylpenicillin and gentamicin once per day for 2 days, then oral amoxicillin twice per day for 5 days (group C)" (Baqui et al., 2015).

Figure 3: Distribution of Delphi Opinion on Reduction of Mortality Due to Pneumonia and Sepsis



Note. Box plot of Delphi expert opinion estimates of reduction in neonatal cause-specific mortality due to pneumonia and sepsis/meningitis. Source: (Zaidi et al., 2011).

Recent studies suggest that rising antimicrobial resistance has made certain antibiotics used to treat neonatal sepsis "redundant"

We believe that antimicrobial resistance is a significant concern in LMICs. Popescu et al. (2020) combine data for five of the countries with the highest burden of neonatal mortality from sepsis and find that over 200,000 neonatal deaths could be attributed to AMR. Along these lines, Thompson et al. (2021) reports in The Lancet that ampicillin has become "redundant for treating neonatal sepsis in LMIC settings."[52] Similarly, the study finds that there is also significant resistance to gentamicin: 70.2% resistance in Gram-negative bacteria.[53] We believe that this recent evidence should lead us to believe that the effectiveness of at least gentamicin is compromised, though we are unsure by how much.

Across 20 low- and middle-income countries, the availability of gentamicin seems poor

Access to appropriate antibiotics for neonatal sepsis remains a significant challenge, especially in LMICs. A 2012 USAID report highlights the lack of injectable antibiotics needed for treating newborns, particularly in remote areas (Coffey et al., 2012). This supply shortage is compounded by the limited availability of suitable formulations for newborns from manufacturers, especially in Asia and sub-Saharan Africa.

[52] We are aware that ampicillin and amoxicillin are related (they are both in the penicillin family), but haven't conducted research into whether resistance to ampicillin would automatically translate to amoxicillin. If so, the appropriateness of the injectable antibiotic toolkit should be rethought.
[53] See: "Gentamicin with 70.2% resistance in Gram-negative bacteria also did not have significant activity" (Thomson et al., 2021).

We are unsure how much to update on a 2012 report. Therefore, to improve our understanding of the situation, we conducted a one-hour search focusing on the availability of gentamicin across LMICs. Knowles et al. (2020) surveyed health facilities across 20 LMICs and found that only slightly over half (56.6%) stocked gentamicin, though we do not know in what preparation.[54] Given the rising concern of AMR, we also explored the availability of amikacin (an antibiotic recommended as an alternative in Thomson et al. (2021)), but a half-hour search yielded no relevant information. Our best guess is that it is not readily available in the quantities needed to replace gentamicin.

Early diagnosis is important to treat newborn sepsis, but this is made difficult by nonspecific symptoms and a lack of reliable tests

Diagnosing sepsis in newborns is challenging because their symptoms are often subtle and can overlap with those of other neonatal conditions (Zea-Vera & Ochoa, 2015). Accurate diagnoses require blood, urine, or cerebrospinal fluid cultures, but these tests can be unreliable for various reasons.[55] Moreover, LMICs often lack sufficient laboratory facilities equipped to handle these samples, which can lead to the underdiagnosis of infections (Popescu et al., 2020).

At the same time, clinicians know that administering antibiotics early to newborns, combined with effective triage and supportive care, can significantly improve survival rates and reduce the risk of chronic health issues (Gleeson et al., 2024). As a result, they have a low threshold to treat, leading to the overdiagnosis of infections, which can contribute to AMR.

In our research, we found no evidence of diagnostic tests for neonatal sepsis that are both cost-effective and accurate, and that can enable detection at or near the point of care (Gleeson et al., 2024), though there seems to be concerted efforts by various organizations to make this a priority, including the WHO, FIND, NEST360 and UNICEF.[56]

Administration of injectable antibiotics is also affected by the availability of equipment like syringes and trained staff, though we think these have become less of an issue recently

Access to quality newborn care is severely limited by shortages in both medical equipment and trained healthcare professionals. A sick newborn's first point of contact is often a village clinic or district hospital, where nurses or community health workers (CHWs) provide the primary care (Popsecu et al., 2020).[57] Evidence regarding the effectiveness of training CHWs to diagnose and treat infections in newborns is weak but promising. A 2022 study (Bang et al., 2022) of

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[54] Chaves and Tadi (2023) suggests that gentamicin comes in three preparations: parenteral (including intramuscular/vaccine), ophthalmic, and topical.
[55] These reasons include: "First, the limited blood volume obtainable in small newborns limits the sensitivity of these tests…Another issue is the low specificity of blood cultures due to microbial contamination during sampling. Causative micro-organisms in neonates often include common skin and mucosal bacteria, because of the unique vulnerability of the newborn immune system; it can therefore be even more difficult to distinguish pathogens from contaminants in blood cultures. With these considerations in mind, falsely positive rates are inversely proportional with age and can reach up to 17% in infants below 12 weeks of age compared with older children." (Popescu et al., 2020).
[56] For a review see Celik et al. (2021). In addition Gleeson et al. (2024) report that, "WHO, with the support of FIND, NEST360 and UNICEF, is planning to develop a target product profile to inform developers and researchers on the minimum and optimal attributes of tests that are well-adapted to the needs in LMIC settings."
[57] While referral to a central hospital for more specialized treatment is sometimes possible, these facilities are often overwhelmed by patient demand and struggle with limited resources (Popescu et al., 2020).

CHWs treating neonatal sepsis in communities in rural India shows that over a 23-year period CHWs correctly diagnosed almost 90% of sepsis cases, and that almost 80% of diagnosed newborns began home-based antibiotic therapy (including injectables). The study reports that the odds of death among neonates whose parents refused treatment were 5x higher than for neonates with home-based treatment by CHWs.

An injectable antibiotics BOTEC on increasing coverage of injectable antibiotics suggests that this might be a promising area for grantmaking

Memirie et al. (2019)[58] estimate that increasing coverage of injectable antibiotics by 20% comes at a cost of $17 per DALY averted—the third most cost-effective among 13 maternal and neonatal interventions they consider. Our research into injectable antibiotics makes us skeptical that the effectiveness numbers are well-calibrated because they are from 2011 and are a result of expert opinion. We conduct a BOTEC to understand how sensitive the cost-effectiveness estimate is to our concerns about effectiveness, available here.

We begin by adjusting the number of DALYs averted each year via two discounts or "haircuts." We use the DALYs averted directly by Memirie et al. (2019), who provide discounted and undiscounted DALYs; they prefer the former. Following OP preference we take the undiscounted number, 105,000 DALYs averted by increasing coverage by 20%. These DALYs are estimated using LiST, which draws on Zaidi et al. (2011) who conclude that injectable antibiotics are roughly 65% effective. These estimates come from Delphi expert opinion on the reduction of neonatal mortality due to injectable antibiotics. We are unsure about how much we should believe these estimates if they come exclusively from expert opinion. We therefore apply a 25% discount.

Next, we attempt to reconcile the effectiveness of the antibiotics with our reading of the AMR evidence. As stated above, recent evidence appears to suggest that the effectiveness of gentamicin–the main injectable antibiotic to treat newborn sepsis–has been compromised. The authors specifically state that gentamicin faces 70.2% resistance in Gram-negative bacteria (Thomson et al., 2021). We do not understand and have not researched what this means specifically for the effectiveness of gentamicin in treating sepsis across the world, though we assume this means it has lost its effectiveness by as much as 70.2%. Because we do not have a good grasp of this number, we add an uncertainty parameter that discounts this haircut by 80%, bringing it to roughly 14%. Taken together, our two haircuts discount DALYs averted by 36%, see spreadsheet with details.

With regard to costs, we simply use the Memirie et al.'s (2019) estimate of the costs of increasing coverage by 20%. We do not know what specifically goes into the calculation of these costs and therefore are unsure how they would have changed since 2019. It is possible that the costs have decreased due to a better supply of antibiotics and equipment, though it is also possible that costs have increased as a result of some unknown supply chain issue. We settle with not adjusting costs but encourage OP to update the model with their beliefs around costs.

Using OP's valuation of a DALY at $100,000, we calculate the social return on investment (SROI) of injectable antibiotics to be over 7,000x. However, as above, our SROI is sensitive to several uncertain parameters in the BOTEC. Specifically, the uncertainty over the effectiveness of gentamicin has large implications for the SROI. If the evidence indeed means that

[58] This is the same resource we reference multiple times above to rank some interventions by cost-effectiveness.

gentamicin has lost effectiveness in treating sepsis by 70%, our model would put its SROI close to 2,500x.

We conclude by speaking to the model's shortcomings. First, we spent only a couple of hours thinking about the basic structure of this model. Additional time could have added complexity to the model. Second, the basic inputs used (costs and benefits) come from Memirie et al. (2019). These inputs are specific to Ethiopia, raising questions as to the generalizability of this analysis. We think, however, that Ethiopia is a reasonable comparison to other countries, especially to those countries with relatively high neonatal mortality rates (NMR) and deaths. Indeed, according to UN estimates , which we collect here, Ethiopia has the 20th-highest NMR in the world, and fourth highest number of neonatal deaths (Hug et al., 2019).[59] Thinking more specifically about costs, GDP per capita may provide a useful sense-check; here Ethiopia is in the 40% percentile when it comes to GDP per capita across sub-Saharan Africa (Wikipedia, 2024). In short, we find Ethiopia to be a sensible reference point, though we remain uncertain about how costs may vary across countries.

[59] The second number is, obviously, a function of sheer size, so we take NMR more seriously when thinking about the type of country that Ethiopia is most similar to (e.g., countries with high—but not extreme—levels of NMR.) Still the fact that Ethiopia has very high numbers of deaths may make it an interesting target for OP.

Contributions and acknowledgments

Tom Vargas and Greer Gosnell jointly researched and wrote this report. Tom Vargas also served as the project lead. Aisling Leow supervised the report. Special thanks to John Firth, Rossa O'Keefe, and Douglas Chukwu for helpful comments on drafts. Thanks also to Shaan Shaikh, Shane Coburn, Thais Jacomassi, and Ula Zarosa for assistance with editing and publishing the report online.

Further thanks to Meika Ball (GiveWell), Andrew Storey and Marta Prescott (Clinton Health Access Initiative), Professor Joy Lawn (London School of Hygiene and Tropical Medicine), and Lara Vaz (Population Reference Bureau) for taking the time to speak with us.

Appendix

Initial Shortlisting Process

We also conducted an initial attempt at shortlisting interventions. This shortlist is tentative and reflects a combined 3 hours of thinking by our team. We were guided by two very rough assessment exercises, the outcomes of which should be considered low confidence and subject to change as we gather more information.

First, we compiled a list of interventions that signaled promisingness based on (at least) one of three criteria, while ruling out any that interviewees suggested we should omit:[60]

1. Relatively strong intervention effects on neonatal and/or maternal mortality (~25% reduction, or higher);
2. Relatively high cost-effectiveness (~$100/DALY or ~$3,000/death averted, or better); or
3. Recommended to us for further investigation by an expert.

Our goal was to identify a shortlist of 5-15 interventions in this initial shortlist to share with OP and to vet in our expert interviews. As such, we eyeballed the intervention effects in the Evidence column of our longlist to get a sense of relatively strong intervention effects. We ultimately landed on ~25% reduction in neonatal and/or maternal mortality, which resulted in our flagging seven interventions as promising. We deprioritized one of these interventions due to GiveWell having reviewed and deprioritized further investigation, and we deprioritized another due to Prof. Joy Lawn's suggestion that traditional birth attendants are less critical given a dramatic decline in home births over the last few decades and remaining TBAs only assisting a few births annually, further dampening potential cost-effectiveness. We note that at the stage in which we undertook this exercise, our longlist contained evidence (likely of varying quality, which we ignored in this exercise) for just 18 interventions, some of which did not report effects in terms of mortality and others of which may not have reported effects in terms of a percentage reduction,[61] so further work would be required to implement these criteria rigorously.

Similarly, we eyeballed the cost-effectiveness numbers we had collected from various sources—primarily [Mangham-Jefferies et al. (2014)]() and [Memirie et al. (2019)]()—for interventions containing information on cost-effectiveness in terms of $/DALY or $/death averted. In total, 19 interventions contained cost-effectiveness information about deaths and/or DALYs averted, three of which overlapped with eligible evidence evaluated in "evidence" criterion above.[62] We noted that the best performer by a large margin was "injectable antibiotics for newborn sepsis" at $17/DALY, while runners-up were closer to $80-$120/DALY. For interventions containing information on cost per death averted, we used ~$3,000/death as our benchmark, based on GiveWells's assessment of "Training for facility-based maternal and neonatal health

[60] For instance, we omitted interventions that GW said they had already investigated and deprioritized, or interventions we shared with other experts that they suggested would not be worth further investigation with sound justification (e.g., relatively low burden associated with the intervention).
[61] For instance, some effects were reported in terms of reductions in deaths per 1,000 live births, or adjusted odds ratios.
[62] The three where both criteria were populated and comparable included: train traditional birth attendants and supply clean delivery kits, hospital-based promotion of breastfeeding, training for facility-based maternal and neonatal health interventions. Otherwise, interventions contained either one or the other criteria. Of all the interventions in our longlist, 21 interventions did not contain usable information for either of these criteria at this early stage.

interventions" as a promising area, which they suggest has an estimated cost-effectiveness around $3,024. Given our hesitations about placing much weight on these papers at this stage,[63] we highlighted all interventions meeting these criteria as 'potentially promising' (eight interventions, highlighted in yellow here) though added "injectable antibiotics for newborn sepsis" to our shortlist, given its superior performance. Note that we have not evaluated the methods of the two cost-effectiveness papers and have taken their estimates at face value for this stage of the research, and we note that Memirie et al. (2019) focuses exclusively on interventions in Ethiopia.

Finally, we added three interventions to our shortlist based on suggestions from Meika Ball of GW.

This process resulted in ten interventions that provide a starting point for comparison against our takeaways from a broader overview of burden across stages of pregnancy and childbirth. To consolidate these results, we created Table A1, which outlines the interventions as well as their target populations (mother, neonate, or both) and which of the above inclusion criteria they passed (highlighted in green):

Table A1: Rough criteria-based intervention shortlist

Intervention	Target population	Evidence	Cost-effectiveness	Interviews
Antenatal corticosteroids for preterm labor	Both			
Package of emergency obstetric and newborn care (BEmONC) and family planning services	Both			
Antenatal care for pregnant women	Both			
Participatory learning and action	Both			
Tranexamic acid (TXA)	Mother			
HSC or oxytocin for postpartum hemorrhage	Mother			
Train traditional birth attendants and supply clean delivery kits	Neonate			
Package of emergency obstetric and newborn care and family planning services	Neonate			
Milk banks	Neonate			
Injectable antibiotics for newborn sepsis	Neonate			

Note. Sourced from this sheet filtered on "RP shortlist = x," indicating that the intervention passed at least one of the criteria and is therefore highlighted in green. The (unfiltered) sheet

[63] We think it's possible that we could have placed more emphasis on cost-effectiveness figures in our shortlisting approach. This would have involved spending further time assessing the underlying evidence, which we were unable to do within the scope of the project.

also indicates where the criteria were less though still potentially promising (yellow), or where one of the three criteria led us to rule out further investigation (red).

Second, given our task of identifying 3 or 4 interventions, we developed additional rules drawing on global data that might help narrow our focus. We took stock of Tables 1 and 2 to understand which stages of pregnancy and disorders are most responsible for deaths and DALYs across mothers and newborns. Two points stand out. One, children's deaths far outnumber mother's deaths (8 to 1), which would suggest that interventions that focus on children or potentially children and the mother are more likely to affect a higher number of deaths/DALYs. Two, across both mothers and children, conditions treated in the antenatal and intrapartum stages account for the vast majority of deaths. This suggests prioritizing interventions that focus on these stages is likely to have higher effects on death and DALYs.

Our narrowed list also appears in the Tentative Shortlist tab in our spreadsheet.

How much do we trust Lives Saved Tool (LiST)'s effectiveness numbers?

In our assessment of the evidence on cost-effectiveness, we noted that various papers we reference, including Memirie et al. (2019) and Mangham-Jefferies et al. (2014), drew on the Lives Saved Tool (LiST) to estimate the effect of given interventions on maternal and neonatal mortality, which then feed into cost-effectiveness models. Due to the importance of this input in generating cost-effectiveness numbers, we conducted a short investigation of LiST.[64] By way of summary, we think LiST overstates the effectiveness of a bundle of interventions. Holding costs constant, any additional intervention will improve the effectiveness of a bundle until it is fully effective (i.e., it reduces mortality to 0).

LiST is a "linear, mathematical model that is deterministic" (Walker et al., 2013). It takes as inputs evidence on the effectiveness of a given intervention (or bundle) and applies it to a given population. According to its website, LiST (2018) uses effectiveness values for over 70 interventions from systematic reviews, meta-analyses, Delphi estimations, and randomized controlled trials based on the Child Health Epidemiology Reference Group (CHERG) guidelines.

LiST models the effect on mortality of scaling up an intervention. For example, if there are 1,000 deaths attributed to a given disease and we introduce a vaccine with 50% efficacy to 50% of the population, LiST estimated mortality will be reduced to 750 (1000-(1000*0.5.*0.5)). LiST's value-add is that it can estimate mortality rates for a bundle of interventions. To do so, it takes the approach outlined above sequentially for each intervention, applying additional interventions to the residual mortality numbers in turn. So, for example, if there are 750 deaths remaining after the first intervention, and we introduce another vaccine with 50% efficacy to 50% of the remaining population, the estimated mortality would be 562 (750-(750*0.5*0.5)). The model assumes no dynamic changes to the cause of death structure, except for those changes in response to increasing intervention coverage (Walker et al., 2013).

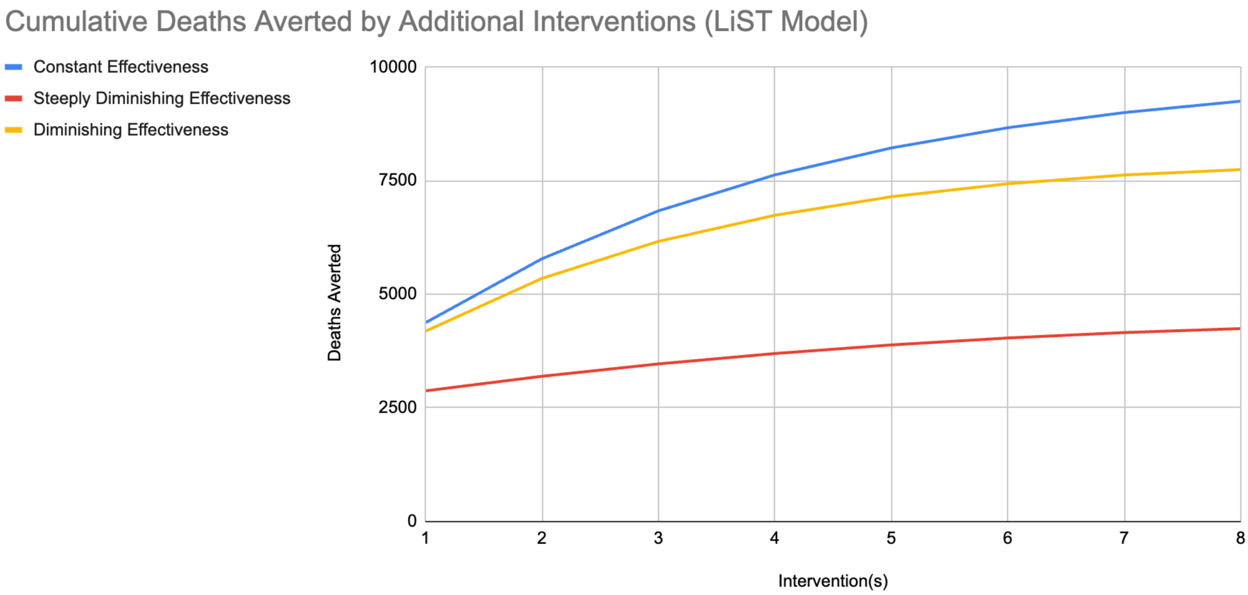
In our view, this model will tend to overstate the effects of bundled interventions. Assuming that each additional intervention is effective (i.e., is known to reduce mortality), then each additional intervention will improve effectiveness until no deaths remain. The blue line in Figure # shows that 10 interventions with 50% effectiveness and 50% coverage (from zero) would result in 9,249 out of 10,000 deaths averted. Setting aside the practical elements of

[64] We spent roughly 1.5 hours doing research on LiST and an additional hour modeling and writing up this section.

implementing 10 interventions concurrently in such a way that we can guarantee coverage and effectiveness, at face value it seems unlikely that each remaining pool of deaths is as easy to avert as earlier ones. We are skeptical this is the case and propose thinking about LiST effectiveness outputs (in the case of bundles) as an upper limit to the effectiveness of the bundle; the applicability of effectiveness evidence should decrease as the number of interventions increases.

We would revise our views if we had misunderstood the model such that there was some sort of penalty applied to each additional intervention, but we do not think this is the case.

Figure A1: Cumulative deaths averted by additional interventions under the LiST model



Note. The simulated dataset is our own. The blue Constant Effectiveness line assumes each additional intervention has 50% effectiveness, and increases coverage to 50% of the remaining population. The yellow Diminishing Effectiveness line assumes each additional intervention has a 5 percentage point reduction in effectiveness from the previous one, starting at 50% effectiveness. The red Steeply Diminishing Effectiveness line assumes that the first intervention has a 50% effectiveness, the second one has a 10% effectiveness, and each additional one thereafter sees a drop in effectiveness of 1 percentage point. We hold coverage increases as constant, but, of course, it would be equivalent to consider coverage increases in the same way as effectiveness, with the same results.

What we would do with more time

- Examine how LiST addresses the order of interventions.
- Review the effect size estimates of Stenberg et al. (2021) Supplementary File 1 (PDF download) and compare against our own.
- Review literature from Elicit search on BEmONC to compare effects with the studies we reviewed in more depth in this report.
- Review GiveWell's facility-based MNH evidence review.
- Interview Patricia Gomez and Michelle Willcox to gain a deeper understanding of BEmONC and possible adjustments to the LDHF approach to improve cost-effectiveness. Note that we attempted to contact these authors 1.5 weeks before completing this research and did not receive a response.
- Follow the Avoiding Maternal Deaths and Disability (AMDD) project at Columbia, which is leading efforts to "re-envision EmONC" (recommended by Dr. Lara Vaz).
- Summarize evidence on the reasons women might not seek access to antenatal care, like in this paper (Dahab & Sakellariou, 2020).
- One of our interviewers suggested that we look at this report (Goalkeepers, 2023) on maternal and neonatal health which might provide good insights into the BMGF thinking on promising interventions.