Supplementary Material

The Economic Burden of Neonatal Sepsis in sub-Saharan Africa

Disability Adjusted Life Years:

Disability Adjusted Life Years (DALYs) secondary to a condition are the product of the incidence (*I*) and the average duration of the disability, weighted by the severity of the disease (the disability weight, DW) on a scale from 0 (perfect health) to 1 (death). For 1 given year during an average lifespan in a population, the total DALYs caused by a condition are

$$DALY = I \ x \ DW \quad \text{(S1)}.$$

Over the life expectancy (*LE*), the DALYs calculated are the sum (integral) of the DALY calculated over the years of life x, or

$$DALYs = \int_{x=0}^{LE} DALY(x)\, dx \quad \text{(S2)},$$

which would assume that the impact of a given disability on every year of life is equivalent.

Table S1: Secondary conditions evaluated in the calculation of DALYs attributable to neonatal sepsis in SSA with associated disability weights and duration.

Condition	Disability Weight	Period of Evaluation
Acute NS	.613	age zero - one week
Death secondary to NS	1	age one week – life expectancy
Survival of NS with NDI	.221	age one week – life expectancy
Survival of NS with cerebral palsy	.170	age one week – life expectancy
Acute PIH secondary to NS	.894	age zero - two weeks
Childhood mortality secondary to PIH	1	age five years – life expectancy
Survival of PIH with NDI	.221	age two weeks – life expectancy

The total DALYs secondary to neonatal sepsis in sub-Saharan Africa for 2014 was calculated as the composite of the disease burden posed by acute NS and the resulting long-term sequelae over a lifetime in the population. Each condition had an associated disability weight (DW) and was applied over a specified duration (Table S1). The number of individuals included for each secondary condition was determined as the product of the incidence of the condition and the total live births in SSA for 2014. The total live births were calculated from the crude birth rate reported by the World Bank [1,2] and were adjusted for the reported infant mortality rate.

Parameter Estimates for Epidemiological Indices and Long-Term Sequelae:

Demographic parameters for sub-Saharan Africa were drawn from World Bank estimates for 2014 reported at the regional level. The percent of the neonatal mortality rate attributed to sepsis reflects the regional range provided by the United Nations Inter-Agency Group for Child Mortality Estimation. The Case Fatality Rate (CFR) was taken as a point estimate from reports by the World Health Organization (WHO young infants study group). Multiple studies indicate that estimates case fatality rates under-report the mortality in the developing world. CFR estimates rely on care-seeking and clinical diagnosis of the underlying pathology, which may be unrealistic in many resource-limited settings[3,4]. Therefore, we report the upper bound (50%) of estimates taken by clinically-confirmed estimates of the CFR associated with neonatal sepsis, as reported by the WHO[5], which are consistent with point estimates reported in other recent literature detailing the global burden of neonatal sepsis[6]. Data detailing the incidence of the long-term sequelae of neonatal sepsis in sub-Saharan Africa are lacking. The incidence and five-year survival of post-infectious hydrocephalus (PIH) were extrapolated from case studies in Uganda [7,8]. The range of incidence values used for neurodevelopmental impairment (NDI) were drawn from literature examining the sequelae of NS in developed and developing-world settings. Table S2 summarizes these data. Three studies, including two systematic reviews, were used to inform the estimates used for the incidence of the various neurodevelopmental sequelae of neonatal sepsis. Two examined the cognitive sequelae of neonatal infection in populations including low birthweight infants. The first, a meta-analysis by Mwanki et al.[4], analyzed 22,161 survivors of intrauterine and neonatal results across 153 studies covering populations from North America, and three from South America, Europe, the western Pacific, southeast Asia, Africa, the eastern Mediterranean. The second reported neuromotor impairment following sepsis in very low-birthweight infants in Brazil [2]. A third review by Bakhuizen[6] et al. provided a meta-analysis summarizing existing international hospital data on short-term and long-term

outcomes of neonatal sepsis, based on 12 studies published between January 2000 and 1 April 2012 and covering 3669 neonates with sepsis.

For each epidemiological parameter that reflected a range, rather than a point estimate, the associated DALYs and corresponding economic estimate were calculated across the full range of reported estimates from the studies included. Thus, our estimates of the health and economic burden of neonatal sepsis reflect the lower and upper bound of available estimates from the literature and accordingly reflect the uncertainty in the parameter estimates. Given the uncertainties involved, we deliberately avoided measures of central tendency (e.g. mean), and sought to encompass the true values within our range estimates.

Age Weighting and Discounting:

The value of a particular year of life (the value of a statistical life-year, VSLY) varies over a lifespan due to age-weighting and discounting. Here we describe the incorporation of age weighting and discounting into the calculation of DALYs.

Age Weighting:

Previous literature indicates the social preference of a year lived in young adulthood to a year lived in early childhood or late adulthood [9]. To model the empirical social preferences in age valuation reported by previous literature [9 10], we introduce an alpha function [11] that models the productive value of a human to society over a lifespan

$$v(x) = Cxe^{-\beta x} \quad \text{(S3)}$$

where *x* is year of life, *C* is the age-weighting correction constant, and *ß* is the age-weighting constant that controls the position of the peak of the function.

Table S2: Reported estimates of incidence in of neurodevelopmental impairment following neonatal sepsis. Estimates are given for survivors of NS, unless otherwise specified.

Secondary Condition	Incidence/Risk	Population	Source
PIH	3-5/1000 live births	Ugandan infants	[7 8]

Cerebral palsy	12.4% (11.1-14.9)[1]	International meta-analyses among low-birthweight infants in low-income and middle-income countries	[12]
	3.2%	Low-birthweight infants in Brazil	[13]
	16.3%	International meta-analyses among low-birthweight infants in low-income and middle-income countries	[14]
General cognitive or neurodevelopmental impairment	30% (26.4-44.4)[1]	International meta-analyses among low-birthweight infants in low-income and middle-income countries	[12]
	47.7%	Brazil, LBW infants	[13]

	35.9%	International meta-analyses among low-birthweight infants in low-income and middle-income countries	[14]
Severe cognitive or learning difficulties	26.4% (22.2-30.00)[1]	International meta-analyses among low-birthweight infants in low-income and middle-income countries	[12]

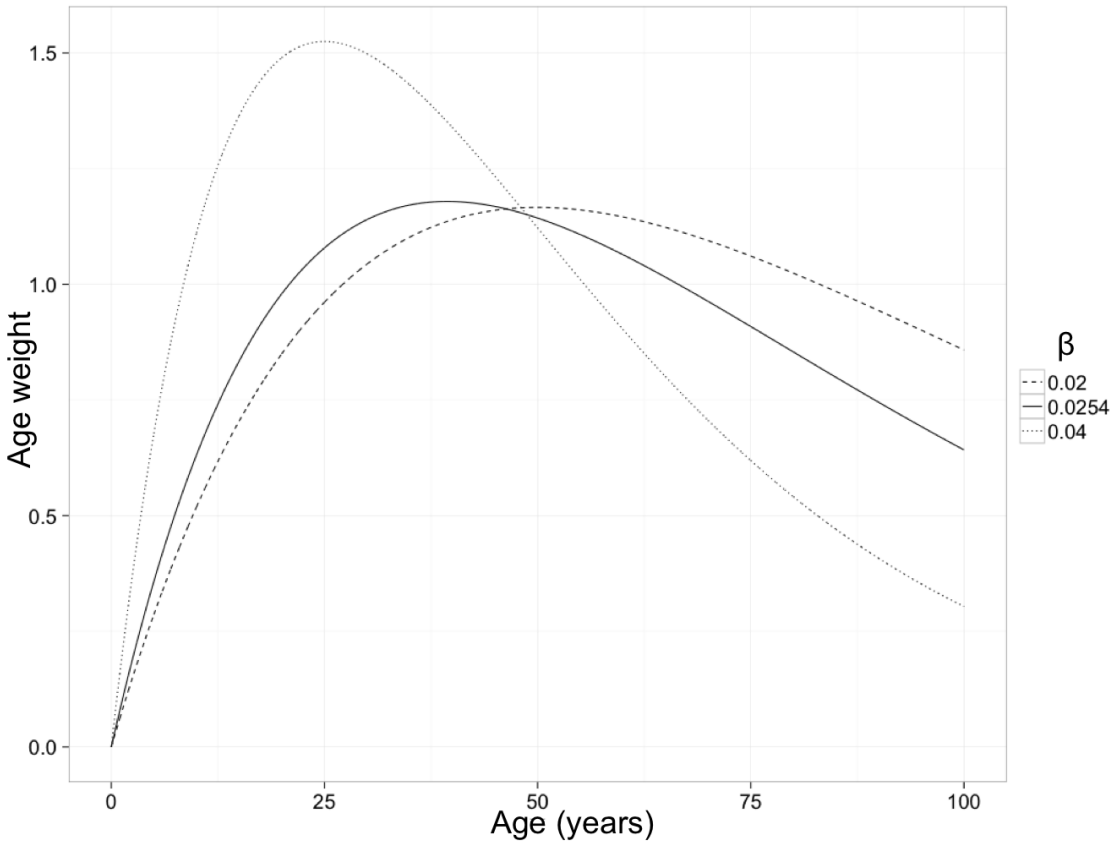
Previous studies indicate that VSLY peaks at 2/3 of life expectancy [15]. By differentiating equation S3 with respect to *x*, we can choose *ß* so that the DALY formula peaks at 2/3 of the average life expectancy of SSA

$ß = \frac{1}{(2/3)LE}$. (S4).

The constant *C* normalizes the area under *v(x)* to unity for a given age-weighting constant *ß*. This ensures that total integrated DALYs remain constant across all values of the age-weighting constant *ß*. The effect of varying *ß* on the age-weighting function is shown in Figure S1.

Figure S1: Age weighting function over 100 years at varying age-weighting constants *ß*. The age-weighting constant *ß* =.0254 represents the value used in this study to achieve a peak in the function at 2/3 life expectancy.

[1] Ranges give 95% confidence intervals reported in the literature



A *C* value is adjusted for a given *ß* value to normalize the area under the age weighting function assuming a maximum standard human life expectancy of 82.5 years [16]. Table S3 below shows the standard *C* and *ß* weights adopted by the WHO.

For this study, the value of *C* was interpolated by fitting a cubic polynomial to the *C* and *ß* values given by Table S3. This approach is consistent with cost-benefit models of other conditions affecting SSA [7 17].

Table S3: Implications of Variation of Choice of Age Weight Parameter on the Age Weighting Function. Adapted from the 2006 Global Burden of Disease and Risk Factors, Table 5.2 [16].

Age-weight parameter *ß*	Age-weight constant *C*	Maximum age-weight	Age of maximum age-weight

.02	0.0634	1.17	50.0
.03	0.1051	1.29	33.3
.04	0.1658	1.52	25.0
.05	0.2487	1.83	20.0
.06	0.3560	2.18	16.7

Discounting:

In order to account for discounting in the VSL methodology, we moderate the DALY function by a term that devalues future years at any given year x following the start of a disabling condition. Discounting is incorporated by

$$g(x) = e^{-r(x-a)} \quad \text{(S5)},$$

where *x* is the year of life, *r* is the discount rate, and *a* is the age of onset of the condition.

We used the discounting rate of 3% that is standard in the health economics literature [10].

Calculation of DALYs for Value of a Statistical Life (VSL):

Evaluated at age *x*, the Disability Adjusted Life Years (*DALY(x)*) for a year *x* secondary to neonatal sepsis (such that *I* = 1 in Equation 1) is given by:

$$DALY(x) = DW * C * xe^{-\beta x} * e^{-r(x-a)} \quad \text{(S6)},$$

where *DW* is the disability weight, *C* is the age-weighting normalization constant, *x* is the current age, *ß* is the age-weighting factor, *r* is the discounting rate, and *a* is the age of onset of disease (*a* is set to 0 for neonatal sepsis).

To evaluate the impact of sepsis over a lifetime, the DALYs of each resulting breakout condition were integrated over the average lifespan for sub-Saharan Africa (LE=59 years)

$$DALYs = \int_a^{LE} DW * C * xe^{-\beta x} * e^{-r(x-a)}\, dx \quad \text{(S7)}.$$

Translation of DALYs to Economic Value:

DALYs provide a measure of the disease attributable to NS over one year in SSA. To evaluate the potential economic benefit of successful intervention, we translate DALYs into a dollar amount.

We use the VSL methodology to determine the constant annual value of each DALY, or the Value of a Statistical Life Year (VSLY). In other words, the economic burden of a disease for a person of a particular age should be the DALY at that age multiplied by an intrinsic "value" associated with that year of life.

Viscusi and Aldy [18] present a model to estimate the value of a statistical life (VSL) in US dollars (USD). The Department of Transportation estimates a standard VSL of $9.2 million for the USA [19]. The VSL of a country in sub-Saharan Africa can be determined comparatively by

$$VSL_{SSA} = VSL_{US} * \left(\frac{Income_{SSA}}{Income_{US}}\right)^{E} \quad \text{(S8)},$$

where VSL_{SSA} is the value of a statistical life for sub Saharan Africa, $Income_{SSA}$ represents the gross national income (GNI) per capita for sub-Saharan Africa, $Income_{US}$ represents the gross national income per capita in the US, and *E* denotes the income-elasticity, a term used to compensate for economic differences in GNI per capita between SSA and the USA. We use three scenarios of income elasticity (*E* = .55, *E*=1 and *E*=1.5) to cover a range of estimates from the literature [18 20].

The value placed on a year of life by VSL methodology varies depending on the year (or age) in the same way as does the DALY function. The value of a statistical life year at a given age x is modeled by:

$$VSLY(x) = VW * Cxe^{-\beta x} \quad \text{(S9)}$$

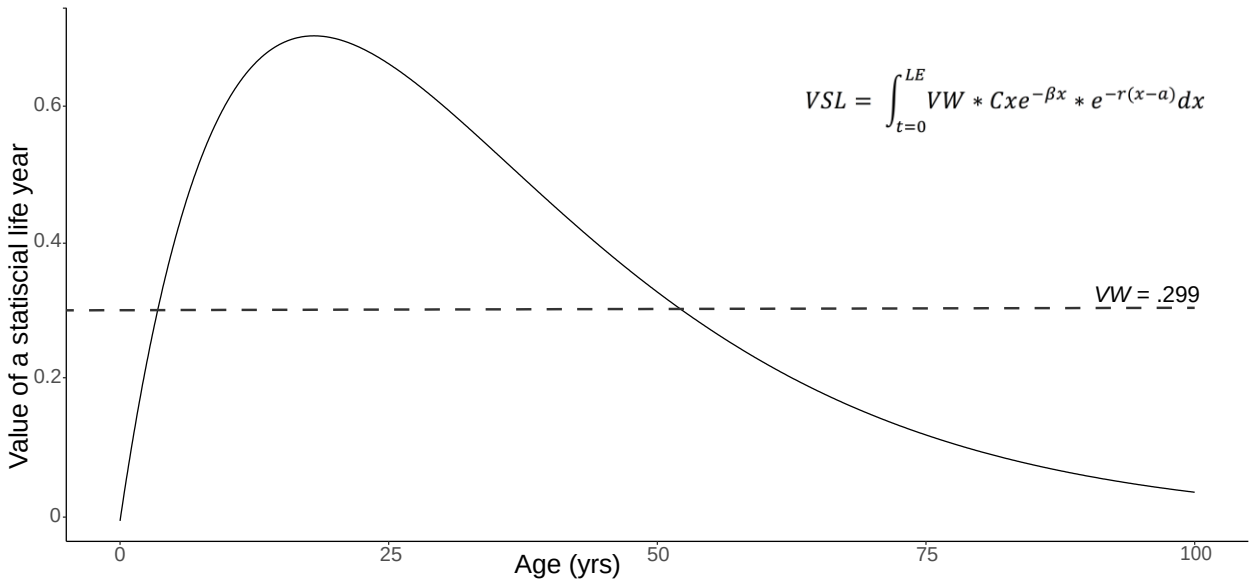
where *VW* is a standard economic value weight, *C* is the age-weighting correction factor, and *ß* is the age-weighting constant. *ß* is again chosen so that the value peaks at an age of two-thirds life expectancy, and *C* normalizes the distribution to incorporate the changing shape of the curve with different age weightings. Considering *VSLY(x)* over a lifetime, we again introduce discounting, using the rate (*r* = 3%) recommended by Murray and Acharaya [10].

The Value of a Statistical Life (VSL) over a lifetime represents the composite of VSLY as a function of age for all ages over a standard life expectancy:

$$VSL = \int_0^{LE} VW * Cxe^{-\beta x} * e^{-r(x-a)} dx \quad \text{(S10)}.$$

In order to determine the economic benefit of averting DALYs, we need a constant dollar value that we can assign to each DALY calculated, regardless of age. Therefore, we seek to remove the age weighting component from (9) and (10) to find the constant *VW* that is standard per year across the curve. The constant *VW* in equations 9 and 10, a "value weight", takes on a similar meaning as the disability weight (*DW*). Much as *DW* describes the burden of disability for one year of life lived with a particular condition, *VW describes* the economic value per year taken as an average along the age-weighted VSLY curve. The constant value weight over a lifespan aggregates the value as the corresponding VSLY curve. *VW* is selected to scale the VSLY curve such that the total area under the curve is equal to the standard VSL calculated from reported estimates. The principle of the value weight is shown in Figure S2. The *VSLY* curve shows the age-varying value curve for each year, while the horizontal line shows the constant value weight *VW* that achieves the same total value (integral) over a lifetime.

Figure S2: Age-Weighted Model VSLY curve with corresponding value weight (*VW* = .299). *VW* plotted over the 100-year span achieves the same area under the curve as the VSLY function and, when incorporated into the VSLY function, assures that the area under the curve is equal to the standard reported VSL.



It becomes clear from an analysis of the units of equation S10 that we can isolate *VW* as a constant. Equation 10 consists of several terms, where *x* is in units of years: *VW*, *C* (the unit-less age-weighting correction factor), $xe^{-\beta x}$, and $e^{-r(x-a)}$ (which is unitless). From basic integration, we know that

$$\int xe^{x}dx = (x-1)e^{x} \quad \text{(S11)},$$

which has units of years. It therefore follows that the equation

$$f(x) = \int_0^{LE} xe^{-\beta x} e^{-r(x-a)}\, dx \quad \text{(S12)}$$

has units of years, and the constant *VW* must have units of dollars per year to achieve the VSL, or dollar value of a statistical lifetime.

Because *VW* and *C* are constant, we can move them out from under the integral as:

$$VSL = VW * C \int_0^{LE} xe^{-\beta x} e^{-r(x-a)}\, dx \quad \text{(S13)}$$

To isolate *VW*, the intrinsic value-per-DALY, we integrate and solve for *VW* by the equation:

$$VW = \frac{VSL}{C} * \frac{(\beta+r)^2}{1-e^{-(\beta+r)*LE}[1+LE(\beta+r)]} \quad \text{(S14)}$$

using the standard VSL value we calculated for a country in SSA. *VW* is the constant shown by the horizontal line in in Figure S2.

Now, the economic burden attributed to a condition by VSL technique becomes

$$Economic\ Burden = VW * DALYs \quad \text{(S15)}$$

as employed here and in previous studies [7 17].

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