Supplementary appendix

First estimates of the global and regional incidence of neonatal herpes infection

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FURTHER DETAILS ON THE METHODS

CALCULATION OF NEONATAL HERPES INFECTION ESTIMATES

Estimates for the number of incident neonatal herpes cases were calculated separately for HSV-2 and HSV-1 and then summed.

Number of incident neonatal HSV-2 infections

Estimates for the annual number of incident neonatal HSV-2 infections by maternal age group during 2010-2015 for each region were calculated by multiplying the total number of prevalent and incident maternal HSV-2 infections during pregnancy by the per-birth risk of neonatal herpes occurring from either a prevalent or incident maternal HSV-2 infection. Specifically, the following equation for the number of incident neonatal HSV-2 infections, $N_{HSV\text{-}2}$, corresponding to maternal year of age a, was used (adapted from [1]):

$$N(a)_{HSV\text{-}2} = B(a) * [(F(a)_{HSV\text{-}2} * r_{prev\_HSV\text{-}2}) + ((k_{HSV\text{-}2} - F(a)_{HSV\text{-}2}) * \lambda_{HSV\text{-}2} * (x_{HSV\text{-}2}/365) * r_{incid\_HSV\text{-}2}))]$$

Number of live births

Fraction of mothers with prevalent HSV-2 infection

Risk of neonatal herpes from a prevalent maternal HSV-2 infection

Fraction of mothers susceptible to HSV-2 infection

Risk of an incident maternal HSV-2 infection occurring near labour in which antibodies have yet to develop

Risk of neonatal herpes from an incident maternal HSV-2 infection which occurs near labour and before antibodies have developed

where:

- $B(a)$ is the annual number of live births at maternal age *a;*
- $F(a)_{HSV\text{-}2}$ is the proportion of women with prevalent HSV-2 infection at age *a*;
- $r_{prev\_HSV\text{-}2}$ is the per-birth risk of neonatal infection from a prevalent maternal HSV-2 infection;
- $k_{HSV\text{-}2}$ is the maximum proportion of women that can be expected to be infected with HSV-2 over a lifetime of exposure;
- $\lambda_{HSV\text{-}2}$ is the incidence of HSV-2 infection per year among (uninfected) women;
- $x_{HSV\text{-}2}$ is the average number of days between HSV-2 infection and the development of protective IgG antibodies (i.e., the window for transmission associated with an incident maternal HSV-2 infection);
- $r_{incid\_HSV\text{-}2}$ is the per-birth risk of neonatal infection from an incident maternal HSV-2 infection which occurs near labour and before antibodies have developed.

The number of births at each maternal year of age, $B(a)$, by region, was estimated using live birth rates by age group of mothers for 2010-2015 from the United Nations Population Division and as appropriate grouping birth rates for different countries and/or different regions used by the United Nations to obtain birth rates for each WHO region[2].

$F(a)_{HSV\text{-}2}$ was obtained from our most recently published global estimates of HSV-2 infection among women aged 15-49 years[3].

To calculate the parameter values for risk we used numbers from a large, multi-centre study conducted in the USA by Brown *et al.* of the effect of maternal viral shedding and serological status on the risk of transmission to the neonate[4]. The value of $r_{prev\_HSV\text{-}2}$ was taken to be 0·022%. At the two study hospitals where HSV serologic testing of pregnant women was done routinely, 13,795 neonates were born to mothers with a prevalent HSV-2 infection (i.e., mothers who were HSV-2 seropositive at delivery). Of these, 3 neonates acquired neonatal herpes, all of which were due to HSV-2. Thus we took the risk of neonatal herpes due to HSV-2 among mothers with a prevalent HSV-2 infection, $r_{prev\_HSV\text{-}2}$, to be 3/13,795 = 0·022%.

The values of $k_{HSV\text{-}2}$ and $\lambda_{HSV\text{-}2}$ were obtained from model fitting during generation of the global and regional estimates of HSV-2 infection[3]. By incorporating both k and λ in the model, the model is able to capture observed patterns of infection by age, such as a rapid increase in prevalence at younger ages followed by a slowing in the increase in prevalence at older ages.

The value of $x_{HSV\text{-}2}$ was taken to be 21 days, based on the median number of days between onset of symptoms and seroconversion based on HerpeSelect HSV-2 ELISA[5,6].

The value of $r_{incid\_HSV\text{-}2}$ was taken to be 7·7%. This value was determined in two steps. First, in the study by Brown *et al.*, the proportion of neonates who acquired neonatal herpes due to HSV-2 among those whose mothers were HSV-2 seronegative but shedding HSV-2 at birth was 22·7% (5 out of 22)[4]. Second, this risk of transmission among mothers with detectable HSV-2 at delivery was then multiplied by 34% for the estimated frequency of HSV-2 isolation in individuals with recent HSV-2 seroconversion in the USA[7] to give a value for the risk of neonatal herpes due to HSV-2 among mothers with an incident HSV-2 infection which occurs near labour and before antibodies have developed, $r_{incid\_HSV\text{-}2}$, of 7·7%.

Number of incident neonatal HSV-1 infections

The number of incident neonatal HSV-1 infections, $N_{HSV\text{-}1}$, was calculated in a similar way:

$$N(a)_{HSV\text{-}1} = B(a) * [(F(a)_{HSV\text{-}1} * r_{prev\_HSV\text{-}1}) + ((k_{HSV\text{-}1} - F(a)_{HSV\text{-}1}) * \lambda_{HSV\text{-}1} * (x_{HSV\text{-}1}/365) * r_{incid\_HSV\text{-}1}))]$$

$F(a)_{HSV\text{-}1}$ was obtained from our published global estimates of HSV-1 infection among women aged 15-49 years[8].

The values of $r_{prev\_HSV\text{-}1}$ were calculated using the study by Brown *et al.*[4]. A total of 31,514 mothers had a prevalent HSV-1 infection at the two hospitals where serologic testing was done routinely, and there were 7 cases of neonatal herpes among them. Two of these cases were due to HSV-1 (Stacy Selke, personal communication). We therefore calculated the risk of neonatal herpes due to HSV-1 among mothers with a prevalent HSV-1 infection, $r_{prev\_HSV\text{-}1}$ (any prevalent HSV-1 infection), as 2/31,514 or 0·0063%. The study by Brown *et al.*[4] was conducted in the USA. The Americas region has the highest proportion of all HSV-1 infections that are genital[8]. We therefore adjusted this risk by the proportion of all HSV-1 infection that is genital in each region relative to the Americas, assuming that a genital HSV-1 infection is more likely to be transmitted to the neonate than an oral HSV-1 infection. This adjustment is not needed for the risk associated with incident HSV-1 infection as it is assumed that any new infection is equally likely to be oral or genital in all regions.

The values of $k_{HSV\text{-}1}$ and $\lambda_{HSV\text{-}1}$ were obtained from model fitting during generation of the global and regional estimates of HSV-1 infection[8].

The value of $x_{HSV\text{-}1}$ was taken to be 25 days, based on the median number of days between onset of symptoms and seroconversion using HerpeSelect HSV-1 ELISA[6].

The value of $r_{incid\_HSV\text{-}1}$ was taken to be 11%, based on results of the study by Brown *et al.*[4]. There were 4 cases of neonatal herpes due to HSV-1 among the 16,876 mothers who were HSV-1 seronegative. Annual HSV-1 incidence (i.e., seroconversion) in initially HSV-1 seronegative women in the USA delivering (twice) over the period 1989-2010 was 3·1% (Amalia Magaret, personal communication, based on data described in [9]). Four cases out of 36 (i.e., 3·1% of 16,876, multiplied by 25/365) gives a value for the risk of neonatal herpes due to HSV-1 among mothers with an incident HSV-1 infection

which occurs near labour and before antibodies have developed, $r_{incid\_HSV\text{-}1}$ (any incident HSV-1 infection), of 11%. We calculated $r_{incid\_HSV\text{-}1}$ slightly differently than for HSV-2 because (1) the numbers of neonatal HSV-1 cases could include oral transmission after birth, and should be applied to all new HSV-1 infections, not just those that are genital; and (2) there is uncertainty in the frequency of viral shedding in individuals with genital HSV-1 seroconversion.

For a list of the values of the key parameters used in the neonatal herpes estimates see Table 1.

SENSITIVITY ANALYSIS

A sensitivity analysis was done varying the values of (a) $r_{prev\_HSV\text{-}2}$; (b) $r_{incid\_HSV\text{-}2}$; (c) $r_{prev\_HSV\text{-}1}$ and (d) $r_{incid\_HSV\text{-}1}$ as follows:

(a) 95% confidence limits around $r_{prev\_HSV\text{-}2}$ were computed in Stata (Stata 13; StataCorp, College Station, Texas, USA) based on a mean proportion of 3/13,795[4] and assuming a binomial distribution for this proportion, generating lower and upper bounds of 0·0045% and 0·064%;

(b) 95% confidence limits around $r_{incid\_HSV\text{-}2}$ were computed as follows: 95% confidence limits around the proportion of neonates who acquired neonatal herpes due to HSV-2 among those neonates whose mothers were HSV-2 seronegative but shedding HSV-2 at birth (5/22)[4] were calculated in Stata assuming a binomial distribution for this proportion, as in (a). These bounds were then multiplied by 34%[7] for the estimated frequency of HSV-2 shedding in individuals with HSV-2 seroconversion and assuming this frequency is true, giving upper and lower bounds for $r_{incid\_HSV\text{-}2}$ of 2·7% and 15·4%. For comparison we provide a second way to compute $r_{incid\_HSV\text{-}2}$: in a study of 2,992 HSV-2 susceptible women in the USA delivering (twice) over the period 1989-2010, an annual HSV-2 incidence of 2·5% was found (Amalia Magaret, personal communication, using data described in [9]). If we multiply 2·5% by the number of HSV-2 seronegative women in the Brown cohort (34,595)[4] and then by 21/365 (the median number of days between onset of symptoms and seroconversion), an estimated 50 women would have acquired HSV-2 and still be seronegative

at delivery. In the study by Brown *et al.* there were a total of 7 cases of neonatal herpes due to HSV-2 in mothers who were HSV-2 seronegative[4]. Seven neonatal herpes cases out of 50 maternal HSV-2 acquisitions gives a value for $r_{incid\_HSV\text{-}2}$ of 14%: this value is higher than our default estimate of 7·7% although within our range for $r_{incid\_HSV\text{-}2}$;

(c) 95% confidence limits around $r_{prev\_HSV\text{-}1}$ were computed as in (a), based on a mean proportion of 2/31,514[4], generating lower and upper bounds of 0·00077% and 0·023%;

(d) 95% confidence limits around $r_{incid\_HSV\text{-}1}$ were also computed as in (a), using a mean proportion of 4/36 (where 36 is calculated from 3·1%[9] (Amalia Magaret, personal communication) of 16,876[4] multiplied by 25/365), generating lower and upper bounds of 3·1% and 26·1%.

The sensitivity of the results was investigated by substituting the default values for the risks of neonatal herpes transmission firstly for the lower bound value for each of the four risks, and then for the upper bound value for each of the four risks (Table 1).

ADDITIONAL RESULTS

Table S1 Number of studies reporting HSV-1 and HSV-2 prevalence in general female populations for the 2012 estimates, by region

Region	% of global births occurring in region	HSV type	Number of studies contributing to estimate							Countries included
			15-19 years	20-24 years	25-29 years	30-34 years	35-39 years	40-44 years	45-49 years	
Americas	11·2	HSV-1	7	9	3	2	3	2	1	Canada, Mexico and United States of America
		HSV-2	12	16	10	6	7	5	4	Brazil, Canada, Columbia, Honduras, Mexico, Peru and United States of America
Africa	24·7	HSV-1	0	1[b]	4	1[b]	1[b]	0	0	Eritrea, Ethiopia, Central African Republic and Zimbabwe
		HSV-2	9	14	19	9	8	1[c]	4	Benin, Burkina Faso, Gabon, Kenya, Malawi, Nigeria, Rwanda, South Africa, Uganda, United Republic of Tanzania, Zambia and Zimbabwe
Eastern Mediterranean	11·0	HSV-1	1[a]	2	1[a]	1[a]	2	1[a]	1[a]	Iran (Islamic Republic of) and Morocco
		HSV-2	1[a]	4	1[a]	3	2	3	0	Iran (Islamic Republic of), Jordan and Morocco
Europe	8·1	HSV-1	1[a]	5	9	9	1[a]	2	1[a]	Croatia, Finland, France, Germany, Greece, Israel, Italy, Poland, Serbia, Switzerland and Turkey
		HSV-2	2	12	13	14	6	6	3	Belgium, Croatia, Finland, France, Germany, Israel, Italy, Poland, Russian Federation, Serbia, Sweden, Switzerland, The Netherlands and Turkey
South-East Asia	26·4	HSV-1	1[a]	3	1[a]	4	1[a]	3	0	Bangladesh, India, Sri Lanka and Thailand
		HSV-2	1[a]	6	6	4	4	3	1[a]	India and Thailand
Western Pacific	18·6	HSV-1	2	5	2	3	4	3	4	Australia, China and Japan
		HSV-2	3	7	8	7	5	2	3	Australia, China, Japan, Papua New Guinea and Republic of Korea
Global	**100**	**HSV-1**	**12**	**25**	**20**	**20**	**12**	**11**	**7**	--
		HSV-2	**28**	**59**	**57**	**43**	**32**	**20**	**15**	

[a]Not used in pooling since N=1; [b]Used in model fitting despite N=1, due to poor data availability.

Table S2 Regional estimates of the number of individuals with existing (prevalent) and new (incident) infection with HSV-2, any HSV-1 and genital HSV-1 for women aged 15-49 years in 2012, in millions[3,8] assuming that 50% of incident HSV-1 infections from age 15 years are genital[10] (percentage of population with prevalent infection shown in parentheses)

Region	HSV-2		Any HSV-1		Genital HSV-1	
	No. with prevalent infection (%)	No. with incident infection	No. with prevalent infection (%)	No. with incident infection	No. with prevalent infection (%)	No. with incident infection
Americas	45 (18)	2·2	152 (62)	2·4	24 (10)	1·2
Africa	81 (38)	3·4	206 (96)	0·0	0·1 (0·0)	0·0
Eastern Mediterranean	19 (13)	0·6	135 (87)	0·3	3 (2)	0·2
Europe	22 (10)	0·9	175 (79)	0·8	11 (5)	0·4
South-East Asia	41 (9)	2·2	306 (63)	0·1	0·7 (0·1)	0·0
Western Pacific	59 (12)	2·6	414 (84)	1·8	24 (5)	0·9

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