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

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Summary

Background Neonatal herpes is a rare but potentially devastating condition with an estimated 60% fatality rate without treatment. Transmission usually occurs during delivery from mothers with herpes simplex virus type 1 (HSV-1) or type 2 (HSV-2) genital infection. However, the global burden has never been quantified to our knowledge. We developed a novel methodology for burden estimation and present first WHO global and regional estimates of the annual number of neonatal herpes cases during 2010–15.

Methods We applied previous estimates of HSV-1 and HSV-2 prevalence and incidence in women aged 15–49 years to 2010–15 birth rates to estimate infections during pregnancy. We then applied published risks of neonatal HSV transmission according to whether maternal infection was incident or prevalent with HSV-1 or HSV-2 to generate annual numbers of incident neonatal infections. We estimated the number of incident neonatal infections by maternal age, and we generated separate estimates for each WHO region, which were then summed to obtain global estimates of the number of neonatal herpes infections.

Findings Globally the overall rate of neonatal herpes was estimated to be about ten cases per 100 000 livebirths, equivalent to a best-estimate of 14 000 cases annually roughly (4000 for HSV-1; 10 000 for HSV-2). We estimated that the most neonatal herpes cases occurred in Africa, due to high maternal HSV-2 infection and high birth rates. HSV-1 contributed more cases than HSV-2 in the Americas, Europe, and Western Pacific. High rates of genital HSV-1 infection and moderate HSV-2 prevalence meant the Americas had the highest overall rate. However, our estimates are highly sensitive to the core assumptions, and considerable uncertainty exists for many settings given sparse underlying data.

Interpretation These neonatal herpes estimates mark the first attempt to quantify the global burden of this rare but serious condition. Better collection of primary data for neonatal herpes is crucially needed to reduce uncertainty and refine future estimates. These data are particularly important in resource-poor settings where we may have underestimated cases. Nevertheless, these first estimates suggest development of new HSV prevention measures such as vaccines could have additional benefits beyond reducing genital ulcer disease and HSV-associated HIV transmission, through prevention of neonatal herpes.

Funding World Health Organization.

Lancet Glob Health 2017; 5: e300–09

Published Online January 30, 2017 http://dx.doi.org/10.1016/S2214-109X(16)30362-X

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Introduction

Neonatal infection with herpes simplex virus (HSV) is a potentially devastating complication of genital herpes during pregnancy. It is rare but is associated with considerable morbidity and mortality: untreated, the case-fatality rate is estimated to be 60%.[1,2] Even with antiviral treatment, mortality rates and lasting neurological impairment remain substantial, especially for neonates with CNS disease (about 30% of cases) and disseminated disease (25% of cases) compared with those with skin, eyes, and mucosa disease (around 45% of cases).[1,2] Neonatal herpes infection is a costly condition since it typically involves a hospital stay, intensive monitoring, intravenous drug treatment, and extensive laboratory testing, and often results in long-term costs associated with disability due to severe neurological sequelae.[3–5]

The majority (>85%) of neonatal herpes infections occur from exposure to HSV type 1 (HSV-1) or type 2 (HSV-2) shed in the genital tract during delivery.[1,6] Neonatal herpes infection due to a prevalent maternal infection is possible but the risk is low because of the presence of protective maternal IgG antibodies, which are able to cross the placenta to afford immunity to the neonate.[1,7] The risk of neonatal herpes infection is considerably greater for incident maternal infections close to term, when virus is

Research in context

Evidence before this study

Neonatal herpes is rare but often leads to death or lifelong disability. Although some surveillance and other studies have assessed neonatal herpes incidence in selected high-income country settings, the global burden has never been estimated to our knowledge. Additionally, no estimates of neonatal herpes incidence seem to exist for resource-poor settings. Particularly in areas with high prevalence of genital infection with herpes simplex virus (HSV) in adults and poor medical infrastructure for prevention, diagnosis, and management, neonatal herpes could be an important under-recognised cause of neonatal morbidity and mortality. Following completion of the first global estimates of HSV-1 infection and updated global estimates of HSV-2 infection in 2015, we estimated the global burden of neonatal herpes incorporating the underlying epidemiology of HSV infections in the population.

Added value of this study

This study presents the first WHO global and regional estimates of the annual number of incident neonatal herpes infections during 2010–15. Our estimation process uses estimates of HSV infection in women by age and WHO region and published mother-to-child transmission risks according to maternal infection characteristics. This process enabled us to demonstrate important differences in the distribution of cases by geographic region, for example, the proportion of cases caused by HSV-1 and the role of incident maternal infection. However, this study also highlights the lack of epidemiological data to inform and validate the estimates in some settings. In particular, because we extrapolate estimates using transmission risk data from the USA, we have probably underestimated neonatal herpes cases in some low-resource settings.

Implications of all the available evidence

Primary data on neonatal herpes incidence in resource-poor settings are crucial to more accurately quantify the mortality and morbidity attributable to neonatal herpes and guide future prevention efforts. Generating first estimates of the global burden of neonatal herpes is a crucial first step in raising awareness of this condition and guiding investment in future interventions such as vaccines and microbicides, by informing the full range and distribution of disease attributable to HSV infection, and therefore, the maximum potential benefit of these interventions.

shed from the genital tract, but maternal IgG antibodies have yet to be produced.[1,7] Intrauterine infection, although highly morbid, accounts for less than 5% of neonatal herpes infections.[1,6] Post-partum infection (around 10% of cases) is thought to be acquired through contact with oral HSV-1 shed by caregivers.[1,6]

Worldwide, HSV-1 and HSV-2 are both highly prevalent.[8–12] HSV-2 is predominantly sexually transmitted and it causes genital herpes. HSV-1 is predominantly orally transmitted and it causes orolabial herpes (ie, cold sores); however, genital HSV-1 infection is possible. In 2012, an estimated 417 million people aged 15–49 years had prevalent HSV-2 infection globally.[8] Since serological tests do not distinguish between orolabial and genital infection, it is difficult to accurately estimate the global number of prevalent genital HSV-1 infections. Estimates for 2012 put the figure among people aged 15–49 years at 140–239 million, depending on the value taken for the proportion of incident HSV-1 infections that are genital after age 15 years.[9] Evidence suggests that the prevalence of genital HSV-1 is increasing in some high-income settings, and that it is becoming an important cause of genital herpes,[13] which may increase rates of neonatal herpes.

The occurrence of neonatal herpes has been difficult to quantify, and the worldwide annual number of cases has never been estimated. Most countries do not require case-reporting of neonatal herpes infections,[4] although a few areas have implemented active surveillance efforts for this disorder.[14,15] Prospective cohort studies that measure incidence have been done only rarely.[7] Without estimates of the numbers of cases of neonatal herpes occurring each year, it is challenging to raise awareness of this devastating infection. Additionally, global estimates are crucial for stimulating efforts to develop HSV vaccines, microbicides, and improved diagnostics and treatment, and for modelling more precisely their potential benefits. Therefore, we present the first set of WHO global estimates of the annual number of incident cases of neonatal herpes infection from HSV-1 or HSV-2 infection in mothers aged 15–49 years during 2010–15.

Methods

To generate estimates of incident neonatal herpes cases worldwide, we used as our starting point the latest WHO global and regional estimates of HSV-1 and HSV-2 prevalence and incidence in women, which were done for 2012 and published in 2015.[8,9] These estimates were informed by comprehensive literature reviews conducted up to February, 2014; full details of the search strategy, methods, and results are reported in the corresponding papers.[8,9] After applying livebirth rates by maternal age group for each WHO region for 2010–15[16] to determine estimates of the prevalence and incidence of maternal HSV infections during pregnancy, we applied published risks of neonatal transmission according to whether the maternal infection was incident or prevalent and type 1 or type 2,[7,17,18] to generate annual numbers of incident neonatal infections according to the equation in figure 1.

Table 1 displays the key parameter values used in the estimates. Estimates of numbers of incident neonatal

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

- $N(a)_{HSV\text{-}s}$: Number of neonatal infections due to HSV-s
- $B(a)$: Number of livebirths
- $F(a)_{HSV\text{-}s}$: Fraction of mothers with prevalent HSV-s infection
- $r_{prev\_HSV\text{-}s}$: Risk of neonatal herpes from a prevalent maternal HSV-s infection
- $k_{HSV\text{-}s} - F(a)_{HSV\text{-}s}$: Fraction of mothers susceptible to HSV-s infection
- $\lambda_{HSV\text{-}s}$: Risk of an incident maternal HSV-s infection occurring near labour in which antibodies have yet to develop
- $r_{incid\_HSV\text{-}s}$: Risk of neonatal herpes from an incident maternal HSV-s infection that occurs near labour and before antibodies have developed

Figure 1: **Equation used to generate annual numbers of incident neonatal infections**

For this equation, $N(a)_{HSV\text{-}s}$ is the annual number of incident neonatal HSV infections corresponding to maternal year of age a due to HSV type s where s=1 or 2; $B(a)$ is the annual number of livebirths at maternal age a;[16] $F(a)_{HSV\text{-}s}$ is the proportion of women with prevalent HSV-s infection at age a;[8,9] $r_{prev\_HSV\text{-}s}$ is the per-birth risk of neonatal infection from a prevalent maternal HSV-s infection;[7] $k_{HSV\text{-}s}$ is the maximum proportion of women that can be expected to be infected with HSV-s over a lifetime of exposure;[8,9] $\lambda_{HSV\text{-}s}$ is the incidence of HSV-s infection per year among (uninfected) women;[8,9] $x_{HSV\text{-}s}$ is the average number of days between HSV-s infection and the development of protective IgG antibodies (ie, the window for transmission associated with an incident maternal HSV-s infection);[19,20] $r_{incid\_HSV\text{-}s}$ is the per-birth risk of neonatal infection from an incident maternal HSV-s infection that occurs near labour and before antibodies have developed.[7,17,18]

	Symbol	Default value	Range used in sensitivity analysis	Reference(s)
HSV-2				
Average number of days between HSV-2 infection and the development of protective IgG antibodies (=transmission window)	$x_{HSV\text{-}2}$	21 days	NA	Ashley et al,[19] Ashley-Morrow et al[20]
Risk of neonatal infection from a prevalent maternal HSV-2 infection	$r_{prev\_HSV\text{-}2}$	0·02%	0·0045% and 0·064%	Brown et al[7]
Risk of neonatal infection from an incident maternal HSV-2 infection that occurs near labour and before antibodies have developed	$r_{incid\_HSV\text{-}2}$	7·7%	2·7% and 15·4%	Brown et al,[7] Phipps et al[17]
HSV-1				
Average number of days between HSV-1 infection and the development of protective IgG antibodies (=transmission window)	$x_{HSV\text{-}1}$	25 days	NA	Ashley-Morrow et al[20]
Risk of neonatal infection from a prevalent maternal HSV-1 infection (any HSV-1 infection)	$r_{prev\_HSV\text{-}1}$	0·0063%	0·00077% and 0·023%	Brown et al[7] and Stacy Selke, personal communication
Risk of neonatal infection from an incident maternal HSV-1 infection (any HSV-1 infection) that occurs near labour and before antibodies have developed	$r_{incid\_HSV\text{-}1}$	11%	3·1% and 26·1%	Brown et al[7] and Amalia Magaret, personal communication, based on data described in Delaney et al[18]

For full details see appendix. HSV=herpes simplex virus. NA=not applicable.

Table 1: **Key parameter values used in the estimates and accompanying range used in the sensitivity analysis**

infections were done for each single year of maternal age (15–49 years) and then summed across each 5-year maternal age group. Separate estimates were produced for each WHO region (the Americas, Africa, Eastern Mediterranean, Europe, Southeast Asia, and Western Pacific) and then summed to obtain global estimates of the number of neonatal herpes infections. A sensitivity analysis was carried out varying the assumed risks of neonatal transmission (table 1). For full details of the methods see appendix.

Role of the funding source

This work was funded by the UNDP/UNFPA/UNICEF/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction. WHO commissioned the study, advised as required, coordinated data requests, helped with redrafts, and approved manuscript submission. KJL had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Findings of the previous HSV estimates that are relevant to the current estimates of neonatal herpes cases are presented in the appendix.[8,9] Globally, of the 139 million livebirths among women aged 15–49 years each year during 2010–15 on average, an estimated 24 million births occurred to women who had either prevalent or incident HSV-2 infection during pregnancy, and 108 million births occurred to women who had either prevalent or incident HSV-1 infection (at any site) during pregnancy (some of which—ie, those births in dually infected mothers—were counted among the numbers with HSV-2 infection).

See Online for appendix

Globally, the annual number of incident neonatal herpes cases during 2010–15 was estimated to be 14 257, of which approximately two-thirds (9911 cases) were due to HSV-2, and a third (4346 cases) were due to HSV-1 (table 2). The global rate of neonatal herpes when averaged across all regions was estimated to be 10·3 per 100 000 livebirths (table 3).

	Maternal age group (years)							Total
	15–19	20–24	25–29	30–34	35–39	40–44	45–49	
Any neonatal herpes								
Americas	484 (3%)	864 (6%)	818 (6%)	565 (4%)	278 (2%)	72 (1%)	10 (<1%)	3091 (22%)
Africa	934 (7%)	1521 (11%)	1282 (9%)	847 (6%)	460 (3%)	168 (1%)	59 (<1%)	5270 (37%)
Eastern Mediterranean	152 (1%)	307 (2%)	269 (2%)	161 (1%)	78 (1%)	26 (<1%)	6 (<1%)	1000 (7%)
Europe	79 (1%)	256 (2%)	312 (2%)	232 (2%)	99 (1%)	20 (<1%)	1 (<1%)	999 (7%)
Southeast Asia	103 (1%)	459 (3%)	402 (3%)	212 (1%)	96 (1%)	30 (<1%)	10 (<1%)	1313 (9%)
Western Pacific	131 (1%)	1123 (8%)	848 (6%)	319 (2%)	119 (1%)	37 (<1%)	6 (<1%)	2583 (18%)
Global total	1884 (13%)	4530 (32%)	3930 (28%)	2336 (16%)	1131 (8%)	353 (2%)	92 (1%)	14 257 (100%)
Neonatal herpes due to a maternal HSV-1 infection								
Americas	358 (8%)	587 (14%)	507 (12%)	320 (7%)	143 (3%)	34 (1%)	4 (<1%)	1954 (45%)
Africa	11 (<1%)	4 (<1%)	2 (<1%)	1 (<1%)	1 (<1%)	0	0	19 (<1%)
Eastern Mediterranean	74 (2%)	113 (3%)	76 (2%)	38 (1%)	17 (<1%)	5 (<1%)	1 (<1%)	325 (7%)
Europe	62 (1%)	174 (4%)	179 (4%)	113 (3%)	42 (1%)	8 (<1%)	0	577 (13%)
Southeast Asia	18 (<1%)	20 (<1%)	8 (<1%)	3 (<1%)	1 (<1%)	0	0	51 (1%)
Western Pacific	99 (2%)	706 (16%)	430 (10%)	131 (3%)	41 (1%)	11 (<1%)	2 (<1%)	1420 (33%)
Global total	622 (14%)	1604 (37%)	1202 (28%)	606 (14%)	246 (6%)	59 (1%)	8 (<1%)	4346 (100%)
Neonatal herpes due to a maternal HSV-2 infection								
Americas	126 (1%)	277 (3%)	310 (3%)	245 (2%)	134 (1%)	38 (<1%)	6 (<1%)	1137 (11%)
Africa	924 (9%)	1517 (15%)	1280 (13%)	846 (9%)	460 (5%)	167 (2%)	59 (1%)	5252 (53%)
Eastern Mediterranean	78 (1%)	194 (2%)	193 (2%)	123 (1%)	61 (1%)	21 (<1%)	5 (<1%)	675 (7%)
Europe	17 (<1%)	82 (1%)	133 (1%)	119 (1%)	57 (1%)	12 (<1%)	1 (<1%)	422 (4%)
Southeast Asia	86 (1%)	439 (4%)	394 (4%)	209 (2%)	95 (1%)	30 (<1%)	10 (<1%)	1262 (13%)
Western Pacific	32 (<1%)	417 (4%)	418 (4%)	188 (2%)	78 (1%)	26 (<1%)	4 (<1%)	1163 (12%)
Global total	1262 (13%)	2927 (30%)	2729 (28%)	1730 (17%)	885 (9%)	294 (3%)	84 (1%)	9911 (100%)

Totals might vary due to rounding. Numbers of cases are given to the nearest integer. It should be noted that all numbers are model estimates. Measurement resolution should not be interpreted as indicative of precision. HSV=herpes simplex virus.

Table 2: **Global and regional estimates of the annual number of cases of neonatal herpes during 2010–15, by HSV type and maternal age group**

Our results showed that Africa contributed the largest proportion (around a third) of neonatal herpes cases to the global total (table 2; figure 2). This result was a consequence of a very high incidence and prevalence of adult female HSV-2 infection in this region (appendix), combined with high number of births (appendix). Our calculations showed that HSV-1 was not an important cause of neonatal herpes in Africa (table 2; figure 2). This finding was based on available data showing a high modelled rate of (oral) HSV-1 infection during childhood and saturation in prevalence by adolescence at almost 100% prevalence in Africa, thus removing potential for further genital HSV-1 infection in adulthood (appendix). HSV-1 did not seem to be a substantial cause of neonatal herpes in Southeast Asia either (table 2; figure 2), again based on available data, which seemed to show saturation in HSV-1 prevalence by adolescence, although the modelled level of saturation in Southeast Asia was much lower than that in Africa (appendix).

By contrast, HSV-1 was estimated to cause more neonatal herpes cases than HSV-2 in the Americas, and also in Europe and Western Pacific (table 2; figure 2). The high numbers of neonatal herpes cases due to HSV-1 in the Americas were due to relatively low rates of childhood HSV-1 infection, with new HSV-1 infections continuing to occur during adulthood (appendix), and the attendant risk to the neonate from genital HSV-1. High rates of genital HSV-1 relative to other regions, combined with moderately high HSV-2 prevalence among women, meant that the Americas was estimated to have the highest overall rate of neonatal herpes in the world: 19·9 per 100 000 livebirths (all births, not just those of infected women; table 3).

The number of neonatal herpes cases by maternal age group increased between the age groups 15–19 and 20–24 years (from 1884 to 4530 cases) and decreased thereafter (table 2). This increase was largely due to the steep rise in number of births by maternal age group. Neonatal herpes incidence decreased with increased maternal age for HSV-1, whereas HSV-2 incidence decreased with increased age from the age groups 15–19 years to 25–29 years but then increased again from 30–34 years until 45–49 years (table 3). These patterns were reflected in an overall trend of increasing proportion of cases due to HSV-2 with maternal age (figure 3).

Patterns in rates are a product of the proportion of women with incident versus prevalent infection, and the risks of transmission associated with each. Neonatal

herpes incidence rates due to HSV-1 declined with increased maternal age because the number of women able to be newly infected with HSV-1 decreased with age, and the risk associated with prevalent maternal HSV-1 infection is low relative to that for incident maternal infection. For HSV-2, global trends masked quite different regional trends. The incidence of neonatal herpes infection increased with maternal age in regions where new maternal HSV-2 infections continued to occur at older ages and prevalence increased with age (Americas, Europe, Southeast Asia, and Western Pacific) but decreased in regions where new infections slowed and maternal HSV-2 prevalence reached saturation at older maternal ages (Africa and Eastern Mediterranean; table 3).

We calculated that the proportion of cases of neonatal herpes was split roughly equally between prevalent versus incident maternal HSV infections, although some regional differences were seen, with most cases attributable to incident maternal infection in Europe, Southeast Asia, Western Pacific, and, most markedly, the Americas (figure 2). However, the relative contribution of prevalent versus incident HSV infection to neonatal herpes cases showed a strong association with maternal age (figure 3).

The number and rate of neonatal herpes is sensitive to the assumed risks of neonatal herpes from a maternal infection (HSV-1 *vs* HSV-2; incident *vs* prevalent infection), reflecting the underlying uncertainty in the values attached to these risks (tables 4 and 5). The variation in numbers of cases and rates between the lowest and highest assumed values was an order of magnitude of approximately 10. When we used the lowest values across all assumptions, the total annual number of cases of neonatal herpes globally during 2010–15 was estimated to be 3703 (2·7 cases per 100 000 livebirths), and when the highest values were used across all assumptions, the total annual number of cases worldwide in 2010–15 was estimated to be 36 415 (26·3 cases per 100 000 livebirths).

	Maternal age group (years)							Overall rate per 100 000 livebirths
	15–19	20–24	25–29	30–34	35–39	40–44	45–49	
Any neonatal herpes								
Americas	22·1	20·6	19·5	18·8	18·4	18·1	18·1	19·9
Africa	18·4	16·2	14·9	14·0	13·5	13·1	12·8	15·4
Eastern Mediterranean	12·4	7·9	5·9	5·0	4·7	4·5	4·4	6·5
Europe	14·9	10·9	8·7	7·6	7·1	6·9	6·8	8·9
Southeast Asia	3·2	3·3	3·6	4·1	4·5	4·9	5·3	3·6
Western Pacific	15·3	1·-3	9·3	8·4	8·1	8·0	8·1	10·0
Global total	14·4	10·3	9·6	9·6	9·7	9·7	9·8	10·3
Neonatal herpes due to a maternal HSV-1 infection								
Americas	16·3	14·0	12·1	10·6	9·5	8·6	7·9	12·6
Africa	0·2	0·04	0·02	0·02	0·02	0·02	0·02	0·05
Eastern Mediterranean	6·1	2·9	1·7	1·2	1·0	0·9	0·9	2·1
Europe	11·7	7·4	5·0	3·7	3·0	2·6	2·4	5·2
Southeast Asia	0·5	0·1	0·07	0·06	0·06	0·06	0·06	0·1
Western Pacific	11·6	7·1	4·7	3·5	2·8	2·5	2·3	5·5
Global total	4·7	3·7	2·9	2·5	2·1	1·6	0·9	3·1
Neonatal herpes due to a maternal HSV-2 infection								
Americas	5·7	6·6	7·4	8·2	8·9	9·6	10·2	7·3
Africa	18·2	16·2	14·9	14·0	13·4	13·1	12·8	15·3
Eastern Mediterranean	6·4	5·0	4·2	3·9	3·6	3·5	3·5	4·4
Europe	3·2	3·5	3·7	3·9	4·1	4·3	4·4	3·8
Southeast Asia	2·7	3·1	3·6	4·0	4·4	4·9	5·3	3·5
Western Pacific	3·7	4·2	4·6	4·9	5·3	5·6	5·9	4·5
Global total	9·6	6·7	6·6	7·1	7·6	8·1	9·0	7·2

Rates are given to 1 decimal place or 2 decimal places for very low rates, to demonstrate trends. It should be noted that all rates are model estimates. Measurement resolution should not be interpreted as indicative of precision. HSV=herpes simplex virus.

Table 3: **Global and regional estimates of the annual incidence of neonatal herpes per 100 000 livebirths during 2010–15, by HSV type and maternal age group**

Discussion

This is the first attempt to quantify the global number of incident neonatal herpes cases. We estimated that every year during 2010–15 over 14 000 cases of neonatal herpes arose from HSV infection in mothers aged 15–49 years worldwide (HSV-1: about 4000; HSV-2: about 10 000), which is equivalent to an annual rate of neonatal herpes of 10·3 per 100 000 livebirths. Our estimates of neonatal herpes cases are highly sensitive to the assumptions made. For example, the numbers of annual cases could be roughly as low as 4000 or as high as 36 000, if the lowest or highest plausible values for all components of neonatal transmission risk are used. Nonetheless, these estimates enable us to gain a first insight into the global picture of neonatal herpes, to compare burden of cases between regions, including the impact of HSV-1 versus HSV-2 and prevalent versus incident maternal infection, and to understand where further data collection is needed. For example, the Americas had the highest estimated regional rate of neonatal herpes, in large part because of the role of HSV-1 infection, which contributed two-thirds of cases to the regional total. This finding is consistent with recent surveillance data from Canada showing that HSV-1 caused 63% of neonatal herpes cases.[15] By contrast, in Africa, almost all cases were due to HSV-2, and high HSV-2 infection rates combined with high birth rates in this region led it to have the highest estimated number of cases globally.

Our global estimated neonatal herpes rate of 10·3 per 100 000 livebirths is consistent with recent estimates from North America, Europe, and Australia using surveillance and administrative data, which have ranged between 2·5 and 13·3 per 100 000 livebirths.[1,5,14,15,21–26] The global number of cases we estimated is similar to what would be expected if neonatal herpes rates from the largest recent population-based estimates from US hospital discharge data (9·6 per 100 000 livebirths) were

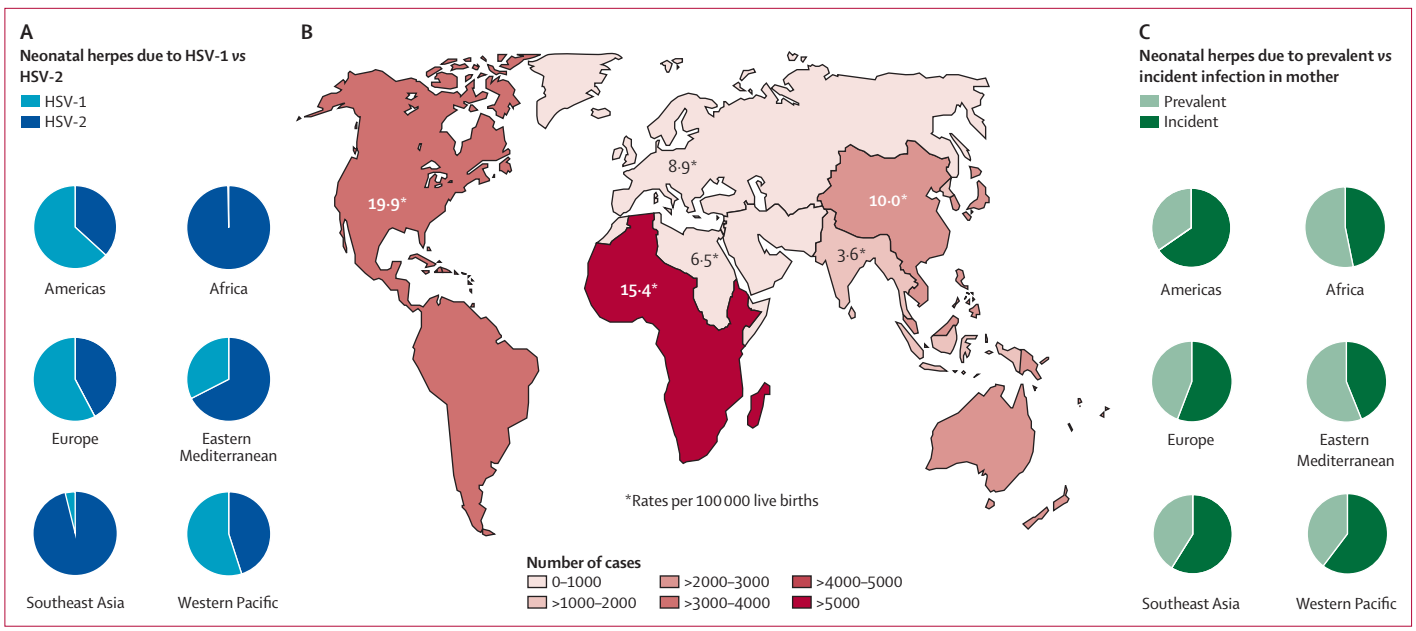

Figure 2: **Estimates of the annual number of cases and rate per 100 000 livebirths of neonatal herpes during 2010–15 (B), and relative contribution of HSV-1 versus HSV-2 (A) and prevalent versus incident HSV infection in the mother (C) to the numbers of cases, by WHO region**

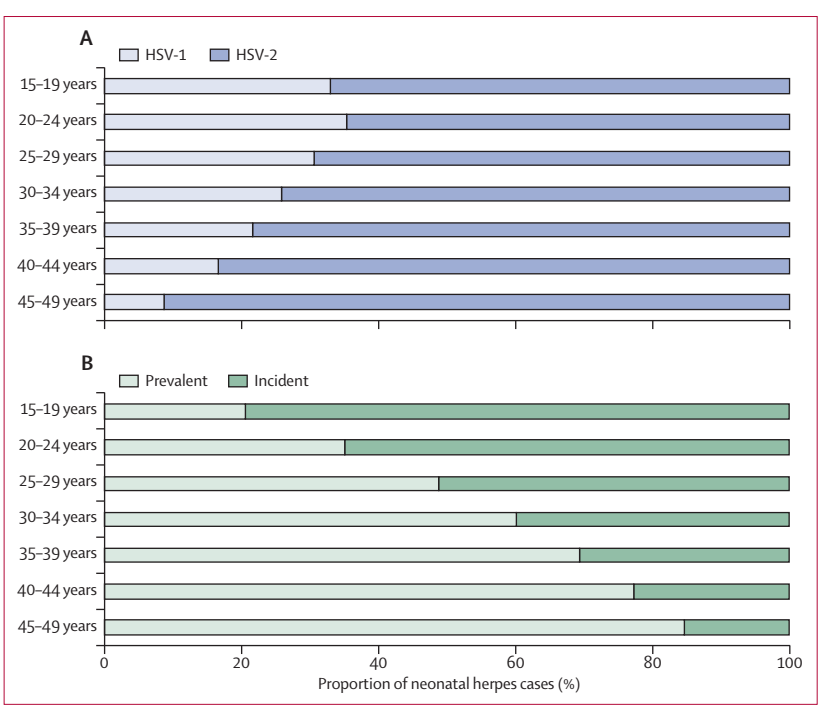

Figure 3: **Percentage of neonatal herpes cases due to (A) HSV-1 versus HSV-2; and (B) prevalent versus incident maternal HSV infection during 2010–15, by age group of the mother**

applied to global births.[5] Our higher estimated rate of 19·9 cases per 100 000 livebirths for the Americas might reflect the challenges of retrospective reviews and difficulty capturing all cases for a condition that has not always had a single clear diagnosis code, and the overall uncertainty inherent in our estimates. A rate of 30·8 per 100 000 livebirths was found in the only large multicentre prospective study of neonatal herpes acquisition, which was the study that informed our underlying neonatal transmission risks.[7] Globally, comparisons with other region-specific rates are made difficult by a general lack of data with regard to neonatal herpes.[27]

These global neonatal herpes estimates provide a starting point for understanding the burden of neonatal herpes worldwide; however, it is likely that we have underestimated the numbers of cases in resource-poor settings. Our estimates rely heavily on data from the USA for parameterising transmission risks. We used numbers from a large, multicentre prospective study in the USA of the effect of maternal HSV shedding and serological status on risk of transmission to the neonate,[7] but this study might not be generalisable to other settings. For example, the overall neonatal transmission risks in this study incorporated routine use of caesarean section when genital lesions were present as well as for other indications, which was shown to substantially reduce the risk of neonatal herpes infection.[7] Thus, the risks and corresponding number of cases could be much higher in settings where caesarean section is not frequently performed. Findings from studies have also shown that HIV infection increases genital HSV-2 shedding frequency and quantity.[28,29] A recent study in South Africa of women in labour found high frequency of HSV-2 shedding at delivery, especially in women co-infected with HIV.[27] Neonatal herpes rates could therefore be even higher in regions with substantial HIV burden in women of reproductive age.[27]

	Maternal age group (years)							Total
	15–19	20–24	25–29	30–34	35–39	40–44	45–49	
Any neonatal herpes								
Americas	130–1193	223–2195	204–2135	136–1512	65–759	16–200	2–28	777–8022
Africa	291–2066	433–3645	336–3264	208–2252	107–1263	38–469	13–167	1425–13126
Eastern Mediterranean	43–360	80–784	63–736	35–465	16–233	5–78	1–19	243–2674
Europe	21–195	65–657	75–836	53–646	22–285	4–58	0–4	241–2680
Southeast Asia	32–231	135–1070	113–971	58–526	25–243	8–78	3–26	374–3146
Western Pacific	38–321	326–2863	243–2250	89–874	33–334	10–107	2–17	741–6767
Global total	552–4365	1225–11213	1000–10193	564–6275	262–3117	79–991	20–262	3703–36415
Neonatal herpes due to a maternal HSV-1 infection								
Americas	90–918	141–1554	116–1388	70–904	30–418	7–102	1–14	454–5928
Africa	3–26	1–11	0–7	0–4	0–3	0–1	0–0	4–53
Eastern Mediterranean	19–187	26–308	15–229	6–125	2–59	1–19	0–5	69–932
Europe	16–157	41–466	38–512	21–346	7–136	1–25	0–2	124–1644
Southeast Asia	5–44	4–58	1–27	0–11	0–5	0–1	0–0	11–146
Western Pacific	25–251	166–1896	91–1238	24–405	7–135	2–39	0–6	315–3972
Global total	157–1584	379–4293	262–3401	122–1796	46–756	10–188	1–26	977–12045
Neonatal herpes due to a maternal HSV-2 infection								
Americas	40–275	82–641	88–747	67–608	35–341	10–98	1–15	323–2724
Africa	289–2040	432–3633	336–3257	207–2248	107–1260	38–468	13–166	1421–13073
Eastern Mediterranean	24–173	54–476	48–508	29–339	14–174	4–59	1–14	173–1742
Europe	5–37	24–191	37–324	32–301	15–148	3–32	0–2	116–1036
Southeast Asia	27–187	131–1012	112–944	57–514	25–239	8–77	3–26	363–2999
Western Pacific	10–70	123–967	118–1012	51–468	20–199	7–68	1–11	329–2795
Global total	395–2781	846–6920	738–6792	442–4479	216–2361	69–802	19–235	2726–24370

Estimates are presented as lowest estimate–highest estimate. Totals might vary due to rounding. Numbers of cases are given in integers. It should be noted that all numbers are model estimates. Measurement resolution should not be interpreted as indicative of precision.

Table 4: **Sensitivity analysis for estimates of annual neonatal herpes cases during 2010–15 by HSV type and maternal age group, varying neonatal herpes transmission risk**

Additionally, these estimates are an attempt to quantify only the number of cases of neonatal herpes, and do not tell us anything about the severity of infection. The clinical course of neonatal herpes, and the case-fatality rate, depend much on whether or not antivirals are given and how promptly, and thus will vary substantially by setting. In areas with less developed medical infrastructure and limited diagnostic testing, neonatal herpes might be missed or mistaken for other serious illnesses, resulting in a higher burden of death and neurological sequelae.[2] If we use a value of 60% for the proportion of neonatal cases that are fatal if left untreated,[1,2] then a rough estimate of the upper limit of the mortality rate due to neonatal herpes is 0·062 per 1000 livebirths, or 8554 neonatal deaths annually given our base case scenario. This number does not of course consider those infants left with lifelong disability, which is also likely to reach the thousands.

Collecting primary data on the incidence of neonatal herpes in resource-poor settings, and especially in sub-Saharan Africa, is therefore crucial. Preliminary data from a validation study of minimally invasive autopsy for evaluating neonatal deaths in Mozambique showed that HSV was the final cause of death in two of 41 neonatal deaths, and was a significant contributing factor in one of 18 stillbirths evaluated (Clara Menendez, personal communication). Although these are small numbers, these data indicate that neonatal herpes could be much under-appreciated as a cause of neonatal mortality in resource-poor settings. Expanded evaluations of neonatal deaths in these settings through the Child Health and Mortality Prevention Surveillance (CHAMPS) network will include HSV testing and will provide critical new data to understand the global impact of neonatal herpes.[30]

Our estimates have several other important limitations relevant to all regions. First, since these estimates of neonatal herpes cases are in turn based on the most recent estimates of prevalence and incidence of HSV-1 and HSV-2 in women aged 15–49 years, the neonatal herpes estimates are affected by the same data availability, generalisability, and quality issues as those affecting the adult estimates.[8,9] Individual studies can have a substantial influence on the estimated burden of maternal infection by region, and, in turn, on the estimates of neonatal herpes cases. Our estimates of genital HSV-1 are particularly uncertain. We assumed a value for the proportion of incident adult HSV-1

	Maternal age group (years)							Overall rate per 100 000 livebirths
	15–19	20–24	25–29	30–34	35–39	40–44	45–49	
Any neonatal herpes								
Americas	5·9–54·4	5·3–52·2	4·9–50·9	4·5–50·3	4·3–50·2	4·1–50·5	4·0–51·1	5·0–51·6
Africa	5·7–40·7	4·6–38·9	3·9–37·9	3·4–37·3	3·1–36·9	2·9–36·7	2·8–36·5	4·2–38·3
Eastern Mediterranean	3·5–29·5	2·0–20·1	1·4–16·2	1·1–14·5	0·9–13·8	0·9–13·5	0·8–13·3	1·6–17·5
Europe	4·0–36·8	2·8–27·9	2·1–23·4	1·7–21·3	1·6–20·4	1·5–20·1	1·4–20·2	2·1–23·9
Southeast Asia	1·0–7·1	1·0–7·6	1·0–8·8	1·1–10·1	1·2–11·4	1·3–12·6	1·3–13·9	1·0–8·6
Western Pacific	4·5–37·6	3·3–28·7	2·7–24·7	2·4–23·1	2·2–22·7	2·2–23·0	2·1–23·5	2·9–26·3
Global total	4·2–33·3	2·8–25·5	2·4–24·8	2·3–25·8	2·3–26·8	2·2–27·3	2·2–27·9	2·7–26·3
Neonatal herpes due to a maternal HSV-1 infection								
Americas	4·1–41·9	3·4–37·0	2·8–33·1	2·3–30·1	2·0–27·7	1·7–25·8	1·5–24·3	2·9–34·1
Africa	0·06–0·5	0·01–0·1	0·00–0·08	0·00–0·07	0·00–0·07	0·00–0·07	0·00–0·07	0·01–0·2
Eastern Mediterranean	1·6–15·3	0·7–7·9	0·3–5·0	0·2–3·9	0·1–3·5	0·1–3·3	0·1–3·3	0·5–6·1
Europe	3·0–29·8	1·7–19·8	1·1–14·3	0·7–11·4	0·5–9·8	0·4–8·9	0·3–8·4	1·1–14·7
Southeast Asia	0·1–1·4	0·03–0·4	0·01–0·2	0·01–0·2	0·01–0·2	0·01–0·2	0·01–0·2	0·03–0·4
Western Pacific	2·9–29·4	1·7–19·0	1·0–13·6	0·6–10·7	0·5–9·2	0·4–8·4	0·3–8·0	1·2–15·4
Global total	1·2–12·1	0·9–9·8	0·6–8·3	0·5–7·4	0·4–6·5	0·3–5·2	0·1–2·8	0·7–8·7
Neonatal herpes due to a maternal HSV-2 infection								
Americas	1·8–12·5	2·0–15·2	2·1–17·8	2·2–20·2	2·3–22·5	2·5–24·7	2·6–26·8	2·2–17·5
Africa	5·7–40·2	4·6–38·8	3·9–37·9	3·4–37·2	3·1–36·8	2·9–36·6	2·8–36·4	4·1–38·2
Eastern Mediterranean	2·0–14·1	1·4–12·2	1·1–11·1	0·9–10·6	0·8–10·3	0·8–10·2	0·7–10·1	1·1–11·4
Europe	1·0–7·0	1·0–8·1	1·0–9·1	1·0–9·9	1·1–10·6	1·1–11·3	1·1–11·8	1·0–9·3
Southeast Asia	0·8–5·8	0·9–7·2	1·0–8·5	1·1–9·9	1·2–11·2	1·3–12·4	1·3–13·7	1·0–8·2
Western Pacific	1·2–8·2	1·2–9·7	1·3–11·1	1·3–12·4	1·4–13·5	1·4–14·6	1·4–15·5	1·3–10·9
Global total	3·0–21·2	1·9–15·8	1·8–16·5	1·8–18·4	1·9–20·3	1·9–22·1	2·0–25·1	2·0–17·6

Estimates are presented as lowest estimate–highest estimate. Rates are given to 1 decimal place, or 2 decimal places for very low rates, to demonstrate trends. It should be noted that all rates are model estimates. Measurement resolution should not be interpreted as indicative of precision.

Table 5: **Sensitivity analysis for estimates of annual neonatal herpes incidence per 100 000 livebirths during 2010-15 by HSV type and maternal age group, varying neonatal herpes transmission risk**

infections that are genital of 50%.[31] To our knowledge, no published studies have estimated this proportion in settings outside the USA; however Africa, Eastern Mediterranean, and Southeast Asia seem to have little new HSV-1 infection in adults,[9] so choice of parameter values for HSV-1 is less influential in these regions.

Second, although the large, multicentre prospective study[7] in the USA from which our transmission risks were taken followed up over 58 000 pregnant women, and represents the best available estimates of risk, the numbers of neonatal herpes cases in this study were extremely small: just 14 cases, which were used to inform our regional and global estimates. Our sensitivity analysis, which incorporated the confidence intervals around the risks from this source study, showed that varying the risks of neonatal transmission due to incident and prevalent maternal infection had a substantial effect on the estimated numbers of neonatal herpes cases.

Finally, HSV incidence could be different between pregnant women and non-pregnant women; however, this is not well understood.[32,33] Acquisition of genital herpes could be lower in pregnant women as a consequence of less frequent sexual activity, particularly during late-stage pregnancy, and lower partner change rates. However, changes in the maternal immune system could increase susceptibility to genital herpes during pregnancy,[34] whereas lower rates of condom use might expose pregnant women to an increased risk of infection.

Genital HSV infections among adolescents and adults are a global public health problem, estimated to affect over half a billion people worldwide.[8,9] Our study is, to our knowledge, the first attempt to quantify and thus better understand the global burden of neonatal herpes. However, data on mother-to-child HSV transmission rates in less industrialised settings are absent, and we have instead relied on single studies of risk from the USA to generate estimates across all regions. In so doing, we might have underestimated neonatal herpes cases in resource-poor settings, perhaps severely. By highlighting the various limitations of these estimates, we hope to stimulate better and more coordinated data collection efforts to improve future estimates. Enhanced case reporting and surveillance where feasible and focused studies to collect prospective data on neonatal herpes

incidence, mortality, and transmission risks will be very valuable. This need is particularly important for settings in sub-Saharan Africa, since low rates of caesarean section and generalised HIV epidemics have the potential to increase the number of neonatal herpes cases to a number well above that estimated here. Additional assessments of the incidence and prevalence of HSV-2 and genital HSV-1 among women, especially in countries outside of North America and Europe, are also needed.

Neonatal herpes has high fatality rates and potential for long-term neurological disability in surviving neonates, but it is rare. This rarity leaves a quandary for appropriate targeting of prevention efforts, and at what cost, for the tens of millions of women who have or are at risk of genital HSV during pregnancy. Prevention efforts have included visual inspection for herpetic lesions at delivery, selective use of caesarean section, potential use of suppressive antiviral therapy in late pregnancy, and behavioural primary prevention messages to reduce transmission of HSV to a susceptible mother in late pregnancy.[35] However, available prevention and treatment options are imperfect, are often expensive, and typically depend on good existing medical infrastructure. Prevention efforts are hampered by the often asymptomatic presentation of maternal HSV infection and the preponderance of cases caused by incident rather than prevalent maternal infection in some settings, as we highlight in these estimates. Additionally, caesarean section has associated risks in itself, especially in settings with poor medical infrastructure. Thus, increasing these procedures in resource-poor settings without clearly defined prevention benefits might do more harm than good.

For these reasons, an effective new vaccine or microbicide developed against genital herpes in adults could have an important and needed benefit in preventing neonatal herpes. Recent scientific advances hold real promise for new HSV vaccine development.[36] The primary targets of such vaccines are prevention of painful genital ulcer disease in tens of millions of adults,[8] reduction in the negative impact on sexual relationships, and reduction in the increased HIV risk associated with genital HSV infection.[37,38] Within the scope of all conditions affecting neonatal health, the current estimates suggest that HSV is not a major contributor, although its impact could be considerably underappreciated in some settings. However, if a vaccine or microbicide in adults could indirectly reduce neonatal transmission, an additional impact on neonatal herpes would not only expand the reach of these interventions, but could also partly mitigate the difficulties in preventing this condition through existing management. Moreover, the high mortality and long-term disability in surviving infants due to neonatal herpes could actually translate into a considerable number of disability-adjusted life-years and costs that could be prevented with a vaccine despite low incidence.[39,40] These global estimates provide a first insight into the potential magnitude of this added benefit. Better primary data on neonatal herpes, particularly in low-resource settings, will help define more precisely the potential global health impact of critically needed new primary prevention measures against HSV infection.[36,41]

Contributors

KJL did the literature review, data extraction, and estimates calculations, and drafted the report. LMN oversaw the study, provided advice as required, and coordinated requests for demographic data. ASM provided statistical input and advised on neonatal herpes natural history parameters. MTM provided statistical advice on the sensitivity analysis. KMET assisted with data checking. PV advised on the modelling aspect. SLG gave advice on the study, its parameterisation and the wider context, and helped redraft the report. All authors contributed to the direction of the work, provided technical expertise, and commented on the drafts.

Declaration of interests

ASM reports grants from National Institutes of Health during the conduct of the study, and personal fees from Immune Design and AiCuris outside the submitted work. LMN has been a full-time employee of the US Centers for Disease Control and Prevention for the past 15 years, but during the time she worked on this project she was seconded to the World Health Organization. All the other authors declare no competing interests.

Acknowledgments

We thank Lauri Markowitz (US Centers for Disease Control and Prevention, Atlanta, GA) for providing additional data, Monica Patton (US Centers for Disease Control and Prevention, Atlanta, GA) for helpful discussion, Anna Wald and Stacy Selke (University of Washington, Seattle, WA, USA) for help with parameterisation from the study by Brown and colleagues 2003, Nathalie Broutet (World Health Organization, Geneva) for commenting on the manuscript drafts, Gretchen Stevens (World Health Organization, Geneva) for statistical advice, Jessica Ho and Ann-Beth Moller (World Health Organization, Geneva) for advising on access to population and births data, and Janet Petitpierre (World Health Organization, Geneva) for helping with the figures. KJL, KMET, and PV thank the National Institute for Health Research (NIHR) Health Protection Research Unit (HPRU) in Evaluation of Interventions at the University of Bristol for research support. This work was funded by the UNDP/UNFPA/UNICEF/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction. WHO commissioned the study, advised as required, coordinated data requests, helped with redrafts, and approved manuscript submission. KJL had full access to all the data in the study and had final responsibility for the decision to submit for publication. SLG is a staff member of the World Health Organization, and LMN was a WHO staff member during her work on this article. KJL received separate funding from the World Health Organization, USAID/PATH, Health Protection Scotland, Sexual Health 24, and the National Institute for Health Research (NIHR) Health Protection Research Unit (HPRU) in Evaluation of Interventions at the University of Bristol during the course of this study. ASM received funding from the National Institutes of Health (NIH P01-A1-030731-23) during the study. PV was additionally supported by the National Institute for Drug Abuse [grant number R01 DA037773-01A1] and the Bill and Melinda Gates-funded HIV Modelling Consortium, and acknowledges further support from the NIHR HPRU in STIs and BBV. These funders had no role in the writing of the report nor the decision to submit it for publication. The authors alone are responsible for the views expressed in this Article and they do not necessarily represent the views, decisions, or policies of the institutions with which they are affiliated, the World Health Organization, the NHS, the NIHR, the Department of Health, or Public Health England.

References

1 Corey L, Wald A. Maternal and neonatal herpes simplex virus infections. *N Engl J Med* 2009; **361:** 1376–85.
2 Kimberlin DW. Herpes simplex virus infections of the newborn. *Semin Perinatol* 2007; **31:** 19–25.
3 Ambroggio L, Lorch SA, Mohamad Z, Mossey J, Shah SS. Congenital anomalies and resource utilization in neonates infected with herpes simplex virus. *Sex Transm Dis* 2009; **36:** 680–85.

4 Handsfield HH, Waldo AB, Brown ZA, et al. Neonatal herpes should be a reportable disease. *Sex Transm Dis* 2005; **32:** 521–25.

5 Flagg EW, Weinstock H. Incidence of neonatal herpes simplex virus infections in the United States, 2006. *Pediatrics* 2011; **127:** e1–8.

6 Gantt S, Muller WJ. The immunologic basis for severe neonatal herpes disease and potential strategies for therapeutic intervention. *Clin Dev Immunol* 2013; **2013**: 369172.

7 Brown ZA, Wald A, Morrow RA, Selke S, Zeh J, Corey L. Effect of serologic status and cesarean delivery on transmission rates of herpes simplex virus from mother to infant. *JAMA* 2003; **289:** 203–09.

8 Looker KJ, Magaret A, Turner KME, Vickerman P, Gottlieb SL, Newman LM. Global estimates of prevalent and incident herpes simplex virus type 2 infections in 2012. *PLoS One* 2015; **1:** e114989.

9 Looker KJ, Magaret A, May MT, et al. Global and regional estimates of prevalent and incident herpes simplex virus type 1 infections in 2012. *PLoS One* 2015; **10:** e0140765.

10 Looker KJ, Garnett GP, Schmid GP. An estimate of the global prevalence and incidence of herpes simplex virus type 2 infection. *Bull World Health Organ* 2008; **86:** 805–12.

11 Looker KJ, Garnett GP. A systematic review of the epidemiology and interaction of herpes simplex virus types 1 and 2. *Sex Transm Infect* 2005; **81:** 103–07.

12 Smith JS, Robinson NJ. Age-specific prevalence of infection with herpes simplex virus types 2 and 1: a global review. *J Infect Dis* 2002; **186** (suppl 1): S3–28.

13 Pena KC, Adelson ME, Mordechai E, Blaho JA. Genital herpes simplex virus type 1 in women: detection in cervicovaginal specimens from gynecological practices in the United States. *J Clin Microbiol* 2010; **48:** 150–53.

14 Handel S, Klingler EJ, Washburn K, Blank S, Schillinger JA. Population-based surveillance for neonatal herpes in New York City, April 2006–September 2010. *Sex Transm Dis* 2011; **38:** 705–11.

15 Kropp RY, Wong T, Cormier L, et al. Neonatal herpes simplex virus infections in Canada: results of a 3-year national prospective study. *Pediatrics* 2006; **117:** 1955–62.

16 United Nations, Department of Economic and Social Affairs, Population Division, Population Estimates and Projections Section. http://esa.un.org/unpd/wpp/unpp/panel_indicators.htm. (accessed April 23, 2014).

17 Phipps W, Saracino M, Magaret A, et al. Persistent genital herpes simplex virus-2 shedding years following the first clinical episode. *J Infect Dis* 2011; **203:** 180–87.

18 Delaney S, Gardella C, Saracino M, Magaret A, Wald A. Seroprevalence of herpes simplex virus type 1 and 2 among pregnant women, 1989–2010. *JAMA* 2014; **312:** 746–47.

19 Ashley RL, Eagleton M, Pfeiffer N. Ability of a rapid serology test to detect seroconversion to herpes simplex virus type 2 glycoprotein G soon after infection. *J Clin Microbiol* 1999; **37:** 1632–33.

20 Ashley-Morrow R, Krantz E, Wald A. Time course of seroconversion by HerpeSelect ELISA after acquisition of genital herpes simplex virus type 1 (HSV-1) or HSV-2. *Sex Transm Dis* 2003; **30:** 310–14.

21 Xu F, Gee JM, Naleway A, et al. Incidence of neonatal herpes simplex virus infections in two managed care organizations: implications for surveillance. *Sex Transm Dis* 2008; **35:** 592–98.

22 Mark KE, Kim HN, Wald A, Gardella C, Reed SD. Targeted prenatal herpes simplex virus testing: can we identify women at risk of transmission to the neonate? *Am J Obstet Gynecol* 2006; **194:** 408–14.

23 Morris SR, Bauer HM, Samuel MC, Gallagher D, Bolan G. Neonatal herpes morbidity and mortality in California, 1995–2003. *Sex Transm Dis* 2008; **35:** 14–18.

24 Mahnert N, Roberts SW, Laibl VR, Sheffield JS, Wendel GD, Jr. The incidence of neonatal herpes infection. *Am J Obstet Gynecol* 2007; **196:** e55–56.

25 Hemelaar SJ, Poeran J, Steegers EA, van der Meijden WI. Neonatal herpes infections in The Netherlands in the period 2006–2011. *J Matern Fetal Neonatal Med* 2015; **28:** 905–09.

26 Jones CA, Raynes-Greenow C, Isaacs D, Neonatal HSV Study Investigators, Contributors to the Australian Paediatric Surveillance Unit. Population-based surveillance of neonatal herpes simplex virus infection in Australia, 1997–2011. *Clin Infect Dis* 2014; **59:** 525–31.

27 Perti T, Nyati M, Gray G, et al. Frequent genital HSV-2 shedding among women during labor in Soweto, South Africa. *Infect Dis Obstet Gynecol* 2014: 258291.

28 Schacker T, Zeh J, Hu HL, Hill E, Corey L. Frequency of symptomatic and asymptomatic herpes simplex virus type 2 reactivations among human immunodeficiency virus-infected men. *J Infect Dis* 1998; **178:** 1616–22.

29 Augenbraun M, Feldman J, Chirgwin K, et al. Increased genital shedding of herpes simplex virus type 2 in HIV-seropositive women. *Ann Intern Med* 1995; **123:** 845–47.

30 The Bill & Melinda Gates Foundation to Fund Disease Surveillance Network in Africa and Asia to Prevent Childhood Mortality and Help Prepare for the Next Epidemic. http://www.gatesfoundation.org/Media-Center/Press-Releases/2015/05/Child-Health-and-Mortality-Prevention-Surveillance-Network (accessed Nov 25, 2015).

31 Langenberg AG, Corey L, Ashley RL, Leong WP, Straus SE. A prospective study of new infections with herpes simplex virus type 1 and type 2. Chiron HSV Vaccine Study Group. *N Engl J Med* 1999; **341:** 1432–38.

32 Brown ZA, Selke S, Zeh J, et al. The acquisition of herpes simplex virus during pregnancy. *N Engl J Med* 1997; **337:** 509–15.

33 Gardella C, Brown Z, Wald A, et al. Risk factors for herpes simplex virus transmission to pregnant women: a couples study. *Am J Obstet Gynecol* 2005; **193:** 1891–99.

34 Jamieson DJ, Theiler RN, Rasmussen SA. Emerging infections and pregnancy. *Emerg infect Dis* 2006; **12:** 1638–43.

35 Gardella C, Brown Z. Prevention of neonatal herpes. *BJOG* 2011; **118:** 187–92.

36 Johnston C, Gottlieb SL, Wald A. Status of vaccine research and development of vaccines for herpes simplex virus prepared for WHO PD-VAC. *Vaccine* 2016; **34:** 2948–52.

37 Freeman EE, Weiss HA, Glynn JR, Cross PL, Whitworth JA, Hayes RJ. Herpes simplex virus 2 infection increases HIV acquisition in men and women: systematic review and meta-analysis of longitudinal studies. *AIDS* 2006; **20:** 73–83.

38 Masese L, Baeten JM, Richardson BA, et al. Changes in the contribution of genital tract infections to HIV acquisition among Kenyan high-risk women from 1993 to 2012. *AIDS* 2015; **29:** 1077–85.

39 Fisman DN, Lipsitch M, Hook EW, Goldie SJ. Projection of the future dimensions and costs of the genital herpes simplex type 2 epidemic in the United State. *Sex Transm Dis* 2002; **29:** 608–22.

40 GBD 2013 DALYs and HALE Collaborators, Murray CJ, Barber RM, et al. Global, regional, and national disability-adjusted life years (DALYs) for 306 diseases and injuries and healthy life expectancy (HALE) for 188 countries, 1990–2013: quantifying the epidemiological transition. *Lancet* 2015; **386:** 2145–91.

41 Gottlieb SL, Low N, Newman LM, Bolan G, Kamb M, Broutet N. Toward global prevention of sexually transmitted infections (STIs): the need for STI vaccines. *Vaccine* 2014; **32**: 1527–35.