

THE LANCET Infectious Diseases

Supplementary webappendix

This webappendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Looker KJ, Welton NJ, Sabin KM, et al. Global and regional estimates of the contribution of herpes simplex virus type 2 infection to HIV incidence: a population attributable fraction analysis using published epidemiological data. *Lancet Infect Dis* 2019; published online Nov 18. [https://doi.org/10.1016/S1473-3099\(19\)30470-0](https://doi.org/10.1016/S1473-3099(19)30470-0).

Appendix: Global and regional estimates of the contribution of herpes simplex virus type 2 infection to HIV incidence: a population attributable fraction (PAF) analysis using published epidemiological data

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FURTHER METHODS

References for FSW and MSM HSV-2 prevalence dataset

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GATHER checklist

Item no.	Item description	Location in manuscript
Objectives and funding		
1	Objectives	Introduction
2	Funding	Role of the Funding Source
Data inputs		
3	Data collation	Methods
4	Inclusion and exclusion criteria	Methods
5	Data sources and characteristics	Methods, Supplementary Dataset and Appendix Further Methods
6	Potential sources of bias	Methods
7	Other data inputs	Methods
8	File of data inputs	Methods, Table 1, Appendix Supplementary Table 1, Supplementary Dataset and Appendix Further Methods
Data analysis		
9	Overview of method	Methods
10	Detailed description of methods	Methods
11	Selection of final model	Methods
12	Model evaluation and sensitivity analysis	N/A
13	Methods for calculating uncertainty	Methods
14	Model code	N/A
Results and discussion		
15	File of estimates	Figure 1 and Tables 2 and 3
16	Estimate uncertainty	Figure 1 and Tables 2 and 3
17	Results interpretation	Discussion
18	Limitations	Discussion

Item number	Checklist item
Objectives and funding	
1	Define the indicator(s), populations (including age, sex, and geographic entities), and time period(s) for which estimates were made.
2	List the funding sources for the work.
Data inputs	
<i>For all data inputs from multiple sources that are synthesised as part of the study:</i>	
3	Describe how the data were identified and how the data were accessed.
4	Specify the inclusion and exclusion criteria. Identify all ad-hoc exclusions.
5	Provide information about all included data sources and their main characteristics. For each data source used, report reference information or contact name/institution, population represented, data collection method, year(s) of data collection, sex and age range, diagnostic criteria or measurement method, and sample size, as relevant.
6	Identify and describe any categories of input data that have potentially important biases (eg, based on characteristics listed in item 5).
<i>For data inputs that contribute to the analysis but were not synthesised as part of the study:</i>	
7	Describe and give sources for any other data inputs.
<i>For all data inputs:</i>	
8	Provide all data inputs in a file format from which data can be efficiently extracted (eg, a spreadsheet rather than a PDF), including all relevant meta-data listed in item 5. For any data inputs that cannot be shared because of ethical or legal reasons, such as third-party ownership, provide a contact name or the name of the institution that retains the right to the data.
Data analysis	
9	Provide a conceptual overview of the data analysis method. A diagram may be helpful.
10	Provide a detailed description of all steps of the analysis, including mathematical formulae. This description should cover, as relevant, data cleaning, data pre-processing, data adjustments and weighting of data sources, and mathematical or statistical model(s).
11	Describe how candidate models were evaluated and how the final model(s) were selected.
12	Provide the results of an evaluation of model performance, if done, as well as the results of any relevant sensitivity analysis.
13	Describe methods of calculating uncertainty of the estimates. State which sources of uncertainty were, and were not, accounted for in the uncertainty analysis.
14	State how analytical or statistical source code used to generate estimates can be accessed.
Results and discussion	
15	Provide published estimates in a file format from which data can be efficiently extracted.
16	Report a quantitative measure of the uncertainty of the estimates (eg, uncertainty intervals).
17	Interpret results in light of existing evidence. If updating a previous set of estimates, describe the reasons for changes in estimates.
18	Discuss limitations of the estimates. Include a discussion of any modelling assumptions or data limitations that affect interpretation of the estimates.

Stevens GA, Alkema L, Black RE, Boerma JT, Collins GS, Ezzati M, et al. Guidelines for Accurate and Transparent Health Estimates Reporting: the GATHER statement. *Lancet*. 2016;388(10062):e19-e23.

Supplementary Table S1 Default parameter values, plausible ranges, and assumptions made on the annual number of incident HIV infections, the proportion of individuals with established HSV-2 infection and with recently-acquired HSV-2 infection, and the RR of HIV acquisition by HSV-2 status used to derive the PAF (%) for each WHO region, by age, sex and risk population

WHO region	Population		Annual number of incident HIV infections due to sexual transmission ^{1,2}			% of individuals with established HSV-2 infection			% of individuals with recently-acquired HSV-2 infection per year			RR of HIV acquisition for established HSV-2 infection			RR of HIV acquisition for recently-acquired HSV-2 infection		
			Default value	Lower UB	Upper UB	Default value	Lower UI	Upper UI	Default value	Lower UB	Upper UB	Default value	Lower CI	Upper CI	Default value	Lower CI	Upper CI
Africa	Women and men	15-49 years	932,000	792,000	1,082,000	31.5%	24.5%	39.8%	1.5%	--	--	2.7 ⁵	2.2	3.4	4.7 ⁵	2.2	10.1
		15-24 years	419,000	356,000	486,934	18.9%	13.9%	26.4%	2.1%	--	--						
		25-49 years	512,000	435,000	595,000	40.6%	32.1%	49.4%	1.0%	--	--						
	Women	15-49 years	529,000	295,000	700,000	38.0%	30.0%	47.1%	1.6%	--	--	2.5 ⁶	1.8	3.4	7.2 ⁶	4.5	11.5
		15-24 years	280,000	156,000	371,000	25.2%	18.6%	33.8%	2.6%	--	--						
		25-49 years	249,000	139,000	330,000	47.1%	38.1%	56.5%	0.8%	--	--						
	Men	15-49 years	403,000	112,000	555,000	25.1%	19.1%	32.6%	1.4%	--	--	3.1 ⁷	2.2	4.3	4.7 ¹⁰	2.2	10.1
		15-24 years	139,000	39,000	192,000	12.6%	9.3%	19.0%	1.6%	--	--						
		25-49 years	264,000	73,000	363,000	34.1%	26.1%	42.4%	1.2%	--	--						
	MSM	15-49 years	66,000 ³	18,000 ³	91,000 ³	69.0% ⁴	45.3% ¹¹	100.0% ¹¹	--	--	--	1.7 ⁸	1.4	2.1	NU	NU	NU
FSWs	15-49 years	47,000 ³	26,000 ³	62,000 ³	81.4%	67.0%	90.4%	--	--	--	1.5 ⁹	0.8	2.7	NU	NU	NU	
Americas	Women and men	15-49 years	140,000	120,000	163,000	14.4%	10.2%	20.5%	0.7%	--	--	2.7 ⁵	2.2	3.4	4.7 ⁵	2.2	10.1
		15-24 years	49,000	42,000	57,000	6.0%	4.2%	9.3%	0.8%	--	--						
		25-49 years	91,000	78,000	106,000	18.3%	13.0%	25.8%	0.7%	--	--						
	Women	15-49 years	40,000	33,000	47,000	18.4%	13.7%	24.6%	0.9%	--	--	2.5 ⁶	1.8	3.4	7.2 ⁶	4.5	11.5
		15-24 years	17,000	15,000	20,000	7.8%	5.7%	11.3%	1.0%	--	--						
		25-49 years	222,000	19,000	26,000	23.2%	17.3%	30.7%	0.8%	--	--						
	Men	15-49 years	100,000	81,000	124,000	10.3%	6.7%	16.3%	0.5%	--	--	3.1 ⁷	2.2	4.3	4.7 ¹⁰	2.2	10.1
		15-24 years	32,000	26,000	40,000	4.3%	2.7%	7.3%	0.6%	--	--						
		25-49 years	69,000	56,000	85,000	13.2%	8.6%	20.7%	0.5%	--	--						
	MSM	15-49 years	62,000 ³	50,000 ³	77,000 ³	37.3%	28.3%	47.2%	--	--	--	1.7 ⁸	1.4	2.1	NU	NU	NU
FSWs	15-49 years	7,000 ³	6,000 ³	9,000 ³	83.7%	72.8%	90.7%	--	--	--	1.5 ⁹	0.8	2.7	NU	NU	NU	
Eastern Mediterranean	Women and men	15-49 years	16,000	13,000	25,000	7.7%	4.7% ¹²	13.4% ¹²	0.3%	--	--	2.7 ⁵	2.2	3.4	4.7 ⁵	2.2	10.1
		15-24 years	4,000	4,000	7,000	5.5%	3.2% ¹²	10.6% ¹²	0.5%	--	--						
		25-49 years	11,000	9,000	18,000	9.0%	5.5% ¹²	15.3% ¹²	0.1%	--	--						
	Women	15-49 years	5,000	4,000	10,000	12.6%	8.0% ¹²	19.8% ¹²	0.4%	--	--	2.5 ⁶	1.8	3.4	7.2 ⁶	4.5	11.5
		15-24 years	2,000	2,000	4,000	9.2%	5.8% ¹²	15.2% ¹²	0.8%	--	--						
		25-49 years	3,000	3,000	6,000	14.5%	9.3% ¹²	22.7% ¹²	0.1%	--	--						
	Men	15-49 years	11,000	8,000	17,000	3.2%	1.8% ¹²	6.5% ¹²	0.1%	--	--	3.1 ⁷	2.2	4.3	4.7 ¹⁰	2.2	10.1
		15-24 years	2,000	2,000	4,000	2.0%	1.1% ¹²	4.9% ¹²	0.2%	--	--						

		25-49 years	8,000	6,000	13,000	3.9%	2.2% ¹²	7.6% ¹²	0.1%	--	--						
	MSM	15-49 years	8,000 ³	6,000 ³	13,000 ³	8.9% ⁴	5.9% ¹¹	13.9% ¹¹	--	--	--	1.7 ⁸	1.4	2.1	NU	NU	NU
	FSWs	15-49 years	3,000 ³	2,000 ³	5,000 ³	17.1%	0.7%	85.7%	--	--	--	1.5 ⁹	0.8	2.7	NU	NU	NU
Europe	Women and men	15-49 years	126,000	120,000	133,000	7.1%	4.0%	12.5%	0.3%	--	--	2.7 ⁵	2.2	3.4	4.7 ⁵	2.2	10.1
		15-24 years	21,000	20,000	22,000	3.1%	1.9%	6.5%	0.4%	--	--						
		25-49 years	105,000	101,000	111,000	8.5%	4.8%	14.8%	0.3%	--	--						
	Women	15-49 years	51,000	46,000	56,000	9.8%	5.2%	17.8%	0.4%	--	--	2.5 ⁶	1.8	3.4	7.2 ⁶	4.5	11.5
		15-24 years	11,000	10,000	12,000	4.5%	2.7%	7.8%	0.5%	--	--						
		25-49 years	40,000	36,000	44,000	11.7%	6.1%	21.4%	0.3%	--	--						
	Men	15-49 years	75,000	71,000	79,000	4.3%	2.8%	7.3%	0.2%	--	--	3.1 ⁷	2.2	4.3	4.7 ¹⁰	2.2	10.1
		15-24 years	10,000	9,000	10,000	1.7%	1.1%	5.3%	0.2%	--	--						
		25-49 years	65,000	62,000	69,000	5.3%	3.4%	8.1%	0.2%	--	--						
	MSM	15-49 years	18,000 ³	17,000 ³	19,000 ³	10.3%	4.6%	21.7%	--	--	--	1.7 ⁸	1.4	2.1	NU	NU	NU
FSWs	15-49 years	8,000 ³	7,000 ³	9,000 ³	66.6%	58.1%	74.1%	--	--	--	1.5 ⁹	0.8	2.7	NU	NU	NU	
South-East Asia	Women and men	15-49 years	124,000	93,000	154,000	7.5%	3.6%	16.0%	0.4%	--	--	2.7 ⁵	2.2	3.4	4.7 ⁵	2.2	10.1
		15-24 years	61,000	46,000	76,000	3.6%	1.5%	8.6%	0.4%	--	--						
		25-49 years	63,000	47,000	78,000	9.6%	4.6%	19.8%	0.3%	--	--						
	Women	15-49 years	45,000	30,000	122,000	8.5%	4.8%	14.8%	0.4%	--	--	2.5 ⁶	1.8	3.4	7.2 ⁶	4.5	11.5
		15-24 years	26,000	17,000	70,000	3.6%	2.0%	6.4%	0.5%	--	--						
		25-49 years	20,000	13,000	53,000	11.0%	6.2%	19.1%	0.4%	--	--						
	Men	15-49 years	79,000	37,000	202,000	6.6%	2.4%	17.0%	0.3%	--	--	3.1 ⁷	2.2	4.3	4.7 ¹⁰	2.2	10.1
		15-24 years	36,000	17,000	91,000	3.7%	1.0%	10.6%	0.4%	--	--						
		25-49 years	43,000	20,000	111,000	8.2%	3.1%	20.4%	0.2%	--	--						
	MSM	15-49 years	27,000 ³	13,000 ³	69,000 ³	18.6%	16.2%	21.2%	--	--	--	1.7 ⁸	1.4	2.1	NU	NU	NU
FSWs	15-49 years	8,000 ³	5,000 ³	22,000 ³	51.8%	37.4%	65.9%	--	--	--	1.5 ⁹	0.8	2.7	NU	NU	NU	
Western Pacific	Women and men	15-49 years	74,000	35,000	133,000	8.0%	4.0%	16.6%	0.4%	--	--	2.7 ⁵	2.2	3.4	4.7 ⁵	2.2	10.1
		15-24 years	17,000	8,000	31,000	3.4%	1.6%	7.6%	0.4%	--	--						
		25-49 years	57,000	27,000	102,000	9.9%	5.0%	20.4%	0.3%	--	--						
	Women	15-49 years	18,000	15,000	22,000	11.9%	6.6%	20.9%	0.5%	--	--	2.5 ⁶	1.8	3.4	7.2 ⁶	4.5	11.5
		15-24 years	5,000	4,000	5,000	5.3%	2.7%	10.2%	0.6%	--	--						
		25-49 years	14,000	11,000	16,000	14.5%	8.1%	25.3%	0.5%	--	--						
	Men	15-49 years	55,000	44,000	65,000	4.3%	1.6%	12.5%	0.2%	--	--	3.1 ⁷	2.2	4.3	4.7 ¹⁰	2.2	10.1
		15-24 years	12,000	10,000	15,000	1.7%	0.6%	5.2%	0.2%	--	--						
		25-49 years	43,000	34,000	50,000	5.4%	2.0%	15.7%	0.2%	--	--						
	MSM	15-49 years	22,000 ³	18,000 ³	26,000 ³	9.5%	5.3%	16.6%	--	--	--	1.7 ⁸	1.4	2.1	NU	NU	NU
FSWs	15-49 years	4,000 ³	3,000 ³	4,000 ³	58.3%	49.4%	66.7%	--	--	--	1.5 ⁹	0.8	2.7	NU	NU	NU	

FSWs: female sex workers; MSM: men who have sex with men; UB: uncertainty bound; CI: confidence interval; NU: not used. Annual number of incident HIV infections due to sexual transmission shown to the nearest thousand. ¹Obtained by subtracting the estimated number of incident HIV infections in PWID from the total number of incident HIV infections, with the exception of incidence for FSWs and MSM. Numbers shown to

2 s. f. ²Not all UB available: unavailable UB derived based on size of available UB for other estimates (as a proportion of the estimate). Numbers shown to 2 s. f. ³Derived by applying the proportion of incident HIV infections estimated to be in FSWs and MSM to the total number of incident HIV infections. ⁴Derived by applying the global mean ratio of prevalence in MSM to prevalence in general population men aged 15-49 years from other WHO regions to the prevalence in general population men 15-49 years in either Africa or Eastern Mediterranean, as applicable. ⁵Estimate for general population women and men applied; all informing studies were from Africa. ⁶Estimate for general population women applied; all informing studies were from Africa. ⁷Estimate for general population men applied; all informing studies were from Africa. ⁸Estimate for MSM applied; all informing studies were from outside Africa. ⁹Estimate for FSWs applied; all informing studies but one were from Africa. ¹⁰Estimate for general population women and men applied (from Africa), as only one informing study was available for men. Blank cell indicates data not available. ¹¹UB derived based on global mean size of UB for MSM (as a proportion of the estimate), truncating at 100%. ¹²UB derived based on global mean size of UB for corresponding data (as a proportion of the estimate).

FURTHER RESULTS

Supplementary Table S2 Estimated global PAF (%) of incident sexually-acquired HIV infection and number of incident HIV infections in 2016 attributable to HSV-2 infection by WHO region, age, sex and risk population

Population		Incident HIV infection from sexual transmission attributable to HSV-2 infection (95%UI)		Population		Incident HIV infection from sexual transmission attributable to HSV-2 infection (95%UI)	
		PAF (%)	Number			PAF (%)	Number
AFRICA GENERAL POPULATION				EUROPE GENERAL POPULATION			
Women	15-24 years	35.2% (25.7%-45.7%)	98,603 (54,963-147,879)	Women	15-24 years	9.2% (5.6%-15.1%)	992 (590-1,606)
	25-49 years	43.1% (29.6%-54.7%)	107,208 (60,240-158,900)		25-49 years	16.5% (8.7%-28.5%)	6,597 (3,405-11,306)
	15-49 years	40.0% (27.9%-50.7%)	211,908 (117,207-318,816)		15-49 years	14.7% (7.8%-25.6%)	7,453 (4,039-13,046)
Men	15-24 years	24.5% (15.4%-36.1%)	34,031 (14,421-61,745)	Men	15-24 years	4.3% (2.0%-8.9%)	413 (195-867)
	25-49 years	43.2% (30.0%-55.8%)	113,906 (48,496-197,659)		25-49 years	10.7% (5.7%-18.0%)	6,955 (3,687-11,792)
	15-49 years	36.6% (24.5%-49.7%)	147,463 (63,349-256,103)		15-49 years	9.0% (4.8%-15.6%)	6,740 (3,523-11,837)
Women and men	15-24 years	28.5% (20.5%-37.8%)	119,706 (82,484-164,550)	Women and men	15-24 years	6.2% (3.4%-11.0%)	1,278 (705-2,235)
	25-49 years	42.1% (33.3%-51.7%)	215,853 (160,874-278,477)		25-49 years	13.4% (7.7%-21.9%)	14,143 (8,116-23,348)
AFRICA KEY POPULATION ANALYSIS				EUROPE KEY POPULATION ANALYSIS			
FSWs		28.9% (0%-60.2%) ¹	13,612 (0-30,418) ^{1,2}	FSWs		25.0% (0%-55.3%) ¹	1,994 (0-4,412) ^{1,2}
MSM		32.6% (3.3%-48.0%) ¹	21,460 (2,222-38,031) ^{1,2}	MSM		6.7% (2.5%-15.5%) ¹	1,212 (444-2,744) ^{1,2}
AMERICAS GENERAL POPULATION				SOUTH-EAST ASIA GENERAL POPULATION			
Women	15-24 years	15.2% (10.1%-22.3%)	2,625 (1,758-3,977)	Women	15-24 years	7.7% (4.7%-13.0%)	1,966 (0-4,818)
	25-49 years	28.6% (18.5%-39.1%)	6,365 (3,987-9,303)		25-49 years	16.1% (8.9%-26.4%)	3,200 (0-7,722)
	15-49 years	24.9% (15.5%-35.1%)	9,830 (6,028-14,755)		15-49 years	13.5% (7.5%-23.0%)	6,127 (0-15,278)
Men	15-24 years	9.9% (5.6%-17.3%)	3,148 (1,681-5,776)	Men	15-24 years	8.4% (3.0%-22.5%)	3,004 (0-10,046)
	25-49 years	22.9% (13.0%-36.0%)	15,693 (8,655-25,874)		25-49 years	15.1% (5.9%-34.8%)	6,546 (0-20,367)
	15-49 years	19.1% (10.9%-30.6%)	19,137 (10,496-32,230)		15-49 years	13.0% (5.2%-29.4%)	10,216 (0-33,057)
Women and men	15-24 years	11.6% (7.7%-17.4%)	5,667 (3,636-8,820)	Women and men	15-24 years	7.2% (3.6%-14.6%)	4,429 (2,089-9,028)
	25-49 years	25.2% (17.5%-34.5%)	22,860 (15,270-31,862)		25-49 years	14.8% (7.3%-26.5%)	9,353 (4,231-17,137)
AMERICAS KEY POPULATION ANALYSIS				SOUTH-EAST ASIA KEY POPULATION ANALYSIS			
FSWs		29.5% (0%-60.4%) ¹	2,125 (0-4,406) ^{1,2}	FSWs		20.6% (0-49.4%) ¹	1,669 (0-5,076) ^{1,2}
MSM		20.7% (12.6%-30.4%) ¹	12,824 (7,269-19,729) ^{1,2}	MSM		11.5% (6.8%-16.9%) ¹	3,114 (0-7,301) ^{1,2}
EASTERN MEDITERRANEAN GENERAL POPULATION				WESTERN PACIFIC GENERAL POPULATION			
Women	15-24 years	15.9% (10.2%-24.6%)	320 (114-593)	Women	15-24 years	10.6% (6.3%-17.5%)	493 (286-828)
	25-49 years	18.5% (10.3%-29.0%)	602 (214-1,153)		25-49 years	19.8% (11.1%-32.1%)	2,728 (1,487-4,418)
	15-49 years	17.6% (9.7%-27.9%)	924 (298-1,855)		15-49 years	17.4% (9.9%-28.5%)	3,197 (1,725-5,589)
Men	15-24 years	4.8% (2.3%-9.7%)	116 (47-253)	Men	15-24 years	4.2% (1.7%-11.6%)	530 (217-1,523)
	25-49 years	7.9% (3.6%-15.8%)	643 (263-1,377)		25-49 years	10.9% (4.0%-25.6%)	4,665 (1,650-11,403)
	15-49 years	6.8% (3.2%-14.3%)	717 (278-1,624)		15-49 years	9.0% (3.4%-21.9%)	4,980 (1,878-12,213)

Women and men	15-24 years	10.1% (6.0%-17.3%)	448 (211-841)	Women and men	15-24 years	6.9% (3.6%-13.4%)	1,176 (359-2,690)
	25-49 years	13.6% (7.7%-21.0%)	1,550 (770-2,850)		25-49 years	15.3% (7.7%-28.3%)	8,675 (2,624-19,597)
EASTERN MEDITERRANEAN KEY POPULATION ANALYSIS				WESTERN PACIFIC KEY POPULATION ANALYSIS			
FSWs		7.9% (0%-45.0%) ¹	203 (0-1,233) ^{1,2}	FSWs		22.6% (0-51.7%) ¹	803 (0-1,880) ^{1,2}
MSM		5.9% (2.9%-10.8%) ¹	474 (189-968) ^{1,2}	MSM		6.2% (2.8%-11.5%) ¹	1,387 (570-2,611) ^{1,2}

UI: uncertainty interval; FSWs: female sex workers; MSM: men who have sex with men. Number of incident HIV infections attributable to HSV-2 infection calculated for each age and sex group separately; therefore estimates do not sum exactly across rows. Number of incident HIV infections attributable to HSV-2 infection not truncated to the nearest thousand as in main manuscript., however these estimates should not be interpreted as being as precise as this suggests. ¹Established HSV-2 infection considered only, and not additionally recently-acquired HSV-2 infection. ²These numbers form a subset of the global numbers, and are not in addition. Estimates based on 2016 HIV incidence data, 2012 HSV-2 infection estimates, RR estimates from a literature review to 2017, and key population breakdown of HIV incidence for 2015.